FDA Executive Summary

Prepared for the October 1, 2014 meeting
of the Gastroenterology and
Urology Devices Panel

P130002
SonaCare Medical, LLC

Sonablate® 450

Division of Reproductive, Gastro-Renal, and Urological Devices
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration

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1. Introduction

The purpose of this summary is to present information relating to the safety and effectiveness of the Sonablate® 450 ("Sonablate" or "Sonablate 450"), manufactured by SonaCare Medical, LLC (SonaCare). This device is designed to use high frequency ultrasound (HIFU) energy to thermally ablate the prostate gland (whole gland treatment) in cases of localized, clinically recurrent prostate cancer after failure of primary external beam radiotherapy (EBRT). Treatment is delivered from a rectal probe under ultrasound visualization.

Currently, there are no legally marketed HIFU devices for the salvage treatment of locally recurrent prostate cancer. Therefore, an advisory panel is being convened to discuss the clinical data collected to demonstrate reasonable assurance of safety and effectiveness in support of PMA approval for this "first of a kind" device.

This Executive Summary for PMA P130002 contains a summary of the device in question, the Sonablate 450, and of the pre-clinical and clinical data available. Areas where the Panel expertise is being solicited are highlighted.

This document, particularly the clinical section:

- Summarizes the study design, results, and conclusions derived from the clinical investigations performed;
- Provides a summary of FDA's evaluation of the proposed device's safety and effectiveness; and
- Discusses the Agency's concerns regarding this application, including:
    - the clinical meaningfulness of comparing the Sonablate 450 effectiveness to a 40% objective performance criteria;
    - the utility of the effectiveness endpoint of 1) absence of biochemical failure combined with 2) negative prostate biopsy at 12 months;
    - the safety profile of this non-surgical device.

The questions to be discussed at the advisory panel meeting will address these fundamental concerns.

Note: Key for fonts used in FDA's Executive Summary:

Times New Roman is used for the general text and information.
Times New Roman bold italics is used for FDA's comments.
Times New Roman bold italics within a box is used to denote questions to the panel.
Times New Roman italics is used for text copied verbatim from the PMA application and published literature.

2. Proposed Indications for Use

The applicant proposes the following indications for use for Sonablate 450:

"The Sonablate® 450 (Sonablate) is indicated for the treatment of biopsy proven recurrent prostate cancer, stage T1c- T2, in patients who have failed primary External Beam Radiation Therapy and have a PSA $\leq$ 10 ng/mL."

The panel will be asked to discuss whether the data from the clinical study support a reasonable assurance of safety and effectiveness for the Sonablate® 450 in the context of the above proposed indication for use.

3. Clinical Background

Prostate cancer is the second most common cause of male cancer-related death in the U.S. It accounts for 3% of all male deaths and is currently the leading soft tissue malignancy in men, representing one third of incident cancer cases. The incidence rate of prostate cancer is estimated to be 146.6 per 100,000 persons in the U.S.[1] Among patients diagnosed with prostate cancer, 46% are reported as being at low risk, 30% at moderate risk, and 24% at high risk, according to the D'Amico classification.[2] The widespread use of PSA screening in clinical practice has resulted in stage migration of the disease leading to an increased proportion of men being diagnosed at earlier stages and lower risk of morbidity and mortality of their disease.

The current choice for men with localized prostate cancer is either therapeutic intervention – consisting primarily of surgery (i.e., radical prostatectomy) or radiation (i.e., EBRT or interstitial brachytherapy) or active surveillance (i.e., regular monitoring with delayed therapy if/when warranted). Other less frequently used therapeutic interventions in this patient population are cryotherapy and hormone therapy.

The natural history of screen-detected prostate cancer remains poorly understood. Autopsy studies have revealed that 50% of men in the age group of 40–49 years harbor prostate cancer. Eighty percent of these cancers are of low volume (<0.5 cm^3) and low grade, and can be classified as "clinically insignificant." The advent of PSA testing and modified prostatic biopsy schemes have led to the diagnosis of cancers that would not otherwise have been diagnosed clinically during a patient's lifetime. There is continued research to develop biomarkers that more accurately characterize a patient's risk beyond that of the currently employed biomarkers of clinical stage, Gleason score, and PSA.[3]

Approximately 30% of all patients treated with definitive radiation therapy for localized prostate cancer experience recurrence of disease. Relapse of prostate cancer occurs in two forms: local disease that is confined to the prostate gland; and loco-regional/metastatic in which disease is identified outside of the anatomic boundaries of the prostate gland. The former is amenable to local salvage intervention while the latter is customarily treated with systemic therapy.

Contemporary definitions of local disease recurrence include a rise in the prostate specific antigen level (PSA) detected during post-treatment monitoring and histologic confirmation of viable tumor on prostate biopsy. The ideal candidate for salvage intervention appears to be the patient with a PSA below10 ng/ml at the time of recurrence and no evidence of metastatic disease on pre-salvage imaging. The patient should also have a life expectancy sufficient to offset the risks that attend salvage interventions.

Salvage therapy for recurrent prostate cancer is the focus of ongoing clinical investigation largely due to the morbidity associated with the administration of historical standards of care. Salvage radical prostatectomy is considered the gold standard for the treatment of organ-confined recurrent prostate cancer following radiation therapy. Less invasive treatment methods that have received contemporary evaluation include cryotherapy, radiofrequency ablation, brachytherapy, photodynamic therapy, and high intensity focused ultrasound.

4. Regulatory History

4.1 IDE Studies

The device was previously manufactured by, US HIFU, LLC, and Focus Surgery, Inc. US HIFU, LLC acquired Focus Surgery. The current sponsor is SonaCare Medical, LLC which acquired US HIFU, LLC.

The sponsor has changed the name of the device from the Sonablate 500 to the Sonablate® 450, because they hold a CE Mark and many international approvals on a device called the Sonablate

500, which has a different version of the software than that of the device used in the U.S. clinical trials.

The applicant initiated an IDE study (G060129) to assess the safety and effectiveness of the Sonablate 500 for the treatment of low risk, localized (T1c/T2a) prostate cancer. Enrollment ended 2011. This study provided initial performance testing, including the mathematical modeling of the temperature rise and dose profiles for the 3 seconds on and 6 seconds off treatment cycle.

The applicant initiated an IDE study (G080057) to assess the safety and effectiveness of the Sonablate 450 for the treatment of localized, clinically recurrent prostate cancer after failure of primary external beam radiotherapy. This study was planned as a multi-center, prospective, non-randomized, single arm clinical trial. The planned primary effectiveness analysis was based on the percentage of patients having (i) biochemical success, defined as achieving a PSA nadir of ≤0.5 ng/mL within 12 months of treatment and (ii) a negative follow-up prostate biopsy at 12 months.

The approved study protocol included a planned interim analysis, to be conducted when 100 patients (of the planned 200 patients) reached the 12 month follow-up.

4.2 Premarket Approval Application

The applicant submitted the current original PMA (P130002) for Sonablate 450 on January 28, 2013, following the planned interim analysis. This application includes the data collected under IDE G080057. The primary safety and effectiveness data are based on the planned interim analysis, conducted when 100 patients reached 12 month follow-up. Additional data were provided for the next 16 patients enrolled, 8 of whom had reached 12 month follow-up.

This Executive Summary is based on information submitted in the original PMA application, as well as information received from the applicant in response to a major deficiency letter issued by FDA.

5. Device Description

5.1 Overview of Components

The Sonablate 450 is a computer-controlled device designed for transrectal delivery of HIFU energy to the prostate for treatment of prostate cancer via thermal ablation. The device makes use of integrated biplanar ultrasound imaging for real-time treatment monitoring, treatment planning, and pre- and post-treatment imaging of the prostate. The system consists of the following main components:

Sonasource Console:

The Sonasource console provides customized control of the system-level functions. The monitor displays all system, patient, imaging, and treatment information via a graphical user interface (GUI). The keyboard and trackball is used for data and user-command entry. The trackball allows the operator to define precisely the dimensions of the treatment zone and to measure the tissue distance from the rectal wall to the center of the treatment zone. The Sonasource console is an assembly of various components and sub-assemblies, which include the Computer Assembly, AC Power System Assembly, DC Power System Assembly, RF Amplifier Assembly, Therapy/Imaging/Radio/Frequency (TIRF) Module Assembly, Transducer Motion Control Subsystem, the Sonablate Safety Circuits, and the Neuro-Vascular Bundle (NVB) detection module (currently disabled in U.S. models).

Sonablate Probe 30/40 (two per unit):

The Sonablate Probe 30/40 (Probe) is designed to provide gray-scale ultrasound images of the prostate and to deliver HIFU treatment pulses to targeted tissue while minimizing damage to intervening tissue. The transducer in each probe has two piezoelectric crystals of different

curvatures with- 30 mm and 40 mm focal lengths on different sides. The dual-sided transducer allows treatment of the entire volume of prostate tissue using only one transrectal probe.

The transducer is an electro-acoustical device that converts electromagnetic radiofrequency (RF) energy to ultrasound energy. The device is constructed of two back-to-back curved surface piezoelectric transducers for focusing without the use of an acoustical lens. Each of the acoustically active surfaces consists of two concentric elements: the inner element being circular of specified radius and the outer element being a roughly annular shape. The inner element is used for imaging. The outer element is used for therapy.

The Probe is an electromechanical device whose design also incorporates two motors (linear and sector), a dedicated closed loop water path, and a thermistor for temperature control. The two position-tracking devices, linear and sector encoders located inside of the Probe, are used as a part of a motor control system and provide the precise positioning of the transducer during the treatment. A cable is used to connect the probe to the console.

In Imaging Mode, the transducer moves in a longitudinal direction to provide linear images of the prostate and oscillates in the transverse plane for sector images. In Therapy Mode, the transducer moves to a particular position and stays at that position while the energy is delivered to the tissue.

Water tubing connects the Probe's water path with the Sonachill unit. During the treatment procedure, the probe tip is inserted into the patient. The Probe tip is filled with water to provide the proper coupling between the transducer and the tissue.

The Probe has built-in temperature control using a thermistor which allows monitoring of the water temperature inside the probe tip and the automatic termination of the treatment if the temperature exceeds 30°C, to reduce the possibility of thermal injury to the rectal wall.

<u>Transducer specifications:</u>

- Two piezoelectric crystals of different curvatures - 30mm and 40mm focal lengths on different sides
- Focal length 3.0 cm±1.0 mm, 4.0 cm±1.0 mm
- Site intensity in the focal zone 1200 to 2000 W/cm^2
- Pulse ON/OFF duration (3 s ON, 6s OFF)
- Frequency 4.0 MHz

Transducer Focal Length	**Default Dosage Value**
4.0 cm	37.0 Watts
3.0 cm	24.0 Watts

HIFU Power Table			
4 cm-focal length		3 cm- focal length	
anterior-middle		posterior	
Rectal Wall Distance (cm)	Watts	Rectal Wall Distance (cm)	Watts
-	-	2.0	21
1.9	32	1.9	22
1.8	33	1.8	22
1.7	35	1.7	23
1.6	36	1.6	24
1.5	37	1.5	25
1.4	38	1.4	26
1.3	39	1.3	26
0.8-1.2	40	1.2	27
-	-	0.8-1.1	28

Sonachill™ Chiller:

The Sonachill is designed to constantly circulate degassed cold water through the probe tip. The water functions to cool the rectal wall and HIFU transducer surface, and to provide ultrasound coupling between the transducer and tissue.

There are two independent fluid pathways. The first fluid path is through the probe and the components of the treatment disposable kit. Fluid entering the Sonachill is isolated from the probe. The second fluid path is located within in the SonaChill and connects the heat exchanger to the pump.

Sonablate Two-Axis Stepper and Probe Arm:

The Sonablate Two-Axis Stepper (Stepper) and the Probe Arm Assembly are used to stabilize the probe in the patient during the HIFU treatment. After insertion of the Probe into the patient, adjustments (in the superior-inferior and anterior-posterior directions) can be

made with the Stepper to optimize the position of the Probe for treatment and in relationship to the prostate Probe Arm Assembly. The Probe Arm Assembly is secured to a bed rail. The Stepper and Probe Arm are locked to hold the Probe in a fixed position for the duration of the treatment.

Probe Accessories:

Probe accessories include the O-Ring Applicator and three o-rings. The probe is covered with a sheath (condom) which is secured by three o-rings using the o-ring applicator.

Cleaning Accessories and Requirements:

Prior to each patient treatment, the Sonablate system is cleaned and sterilized. Two separate kits, the Sonachill Cleaning Kit and the Probe Cleaning Tubing Kit, consisting of disposable items are utilized for cleaning and sterilizing the probe and Sonachill chiller. These processes require the use of cleaning agents along with isopropyl alcohol and sterile water for flushing as the final step to remove any remnants of cleaning solutions. For the probe cleaning, brushes are also utilized for the hard-to-reach areas of the probe to ensure adequate cleaning. Following cleaning and sterilization, a pre-sterilized Procedure Treatment Disposable Kit is used for the dual loop water path between the probe and chiller. The cleaning accessories for the Sonablate system include the Sonachill Cleaning Kit, Probe Cleaning Tubing Kit, and Procedure Treatment Disposable Kit.

Required cleaning and Sterilization of Components:			
System Component	Cleaning	Steam Sterilization	Ethylene Oxide Sterilization
Probe	Yes	No	Yes
Probe Arm	Yes	Yes	No
Stepper	Yes	Yes	No
Console	Yes	No	No
Chiller	Yes	No	No

5.2 Principle of Operation

HIFU causes the thermal destruction of tissue, or thermal ablation. Tissue absorption of ultrasound energy results in heat buildup, which increases to the point of cell death via coagulative necrosis.

Damage to intervening tissue is minimized by the precise delivery of ultrasound waves. The ultrasound waves converge at the focal point and dissipate thereafter. The tightly focused ultrasound energy within the transducer's focal point is applied for short periods that are followed by rest periods.

The HIFU lesion is controlled by focusing the ultrasound energy using spherically-shaped HIFU transducers. Focusing the ultrasound waves allows the targeting of tissue at a specific distance from the transducer, while minimizing damage to intervening and surrounding tissue

Damage to surrounding tissue from heat buildup is mitigated by monitoring continuously the changes that occur in tissue from the delivery of the heat. In general, destruction caused by the concentrated focus of the ultrasound waves results in hyperechoic changes in the tissue (cavitation). These hyperechoic changes are referred to as 'popcorn' and are differentiated on a 1-3 grading scale as noted below:

- Grade 1 small, non-overlapping hyperechoic regions contained within the treatment zone
- Grade 2 contiguous hyperechoic regions (connecting to adjacent treatment sites) within the treatment zone
- Grade 3 large hyperechoic regions or microbubble clouds appearing outside the treatment zone

In addition, the rest time between therapy pulses allows time for heat to dissipate, thereby reducing the risk of damage. Tissue may also be protected by mechanisms of blood perfusion, which can conduct heat away from tissue to be preserved.

The energy delivered at the treatment focal point (site intensity) will be lower than the energy emitted by the HIFU transducer in the free field (free-field intensity), due to absorption of energy (attenuation) and loss of strength as the sound waves travel through tissue.

Prostate tissue depth affects attenuation and is critical to the delivery of appropriate intensity levels at the targeted tissue to create tissue necrosis. Tissue ablation due to the thermal process for this transducer has been modeled by the transient bioheat transfer equation (BHTE), which describes temperature distributions both spatially and temporally, given certain tissue properties and ultrasound stimuli.

Using the prostate-specific and Sonablate-specific parameters, the BHTE and thermal dose models (solved numerically) produce typical results for a 3-second HIFU "ON" exposure with a

6-second HIFU "OFF" cooling time, with a total acoustic power level of 37 W (default power setting).

During treatment, the temperature of the prostate tissue in the focal zone is elevated up to 90° C for < 3 seconds while minimizing elevated temperatures in the intervening tissue between the transducer and the focal zone. The HIFU beam is kept on for 3 seconds; tissue heat conduction leads to a thermal lesion of larger volume. The site intensity in the focal zone ranges from 1200 to 2000 W/cm^2 depending on the dosage setting, probe focal length, and tissue depth. The resulting lesion volume is approximately 108 mm^3. The HIFU ON time of 3 seconds is followed by an OFF time of 6 seconds to cool down the transducer surface and avoid overheating tissue outside the targeted zone. Larger tissue lesion volume is generated by placing overlapping lesions adjacent to each other through precise movements of the transducer in two perpendicular planes (longitudinal and transverse planes) controlled by the console. During the OFF time, the transducer is positioned to the next treatment site. The system takes updated real-time ultrasound images of the prostate in both longitudinal and transverse planes and displays them on the screen for real-time treatment monitoring. Multiple lesions are created to treat the entire selected tissue volume of the prostate.

5.3 Clinical Usage

To prepare for treatment, the probe tip is covered with a probe sheath and secured with o-rings. The Sonachill, probe and tubing is primed with distilled, degassed water chilled to 16° C. Air bubbles are removed from probe tip, water reservoir and water path tubing. After appropriate induction of anesthesia, a Foley catheter and a suprapubic catheter are inserted. Using ultrasound gel, the probe is introduced into the patient's rectum.

Pre-treatment imaging of the prostate is performed to ensure proper position of the probe. The prostate is measured by the physician, including maximum prostatic height, rectal wall thickness, anterior-posterior diameter (AP diameter is the length from apex to base in transverse view), prostate volume. The prostate scan is done automatically and creates 15 transverse images. The Physician defines the number of treatment zones.

The treatment is performed from anterior to posterior towards the rectal wall. Overlaps should be planned in the anterior zones. The 4.0 cm transducer is used to treat the anterior zone, then the center of the prostate unless the rectal wall is more than 2.0 cm away from the transducer. If the rectal wall is more than 2.0 cm from the transducer, the 3.0 cm transducer is used. The posterior zone of the prostate is treated using the 3.0 cm transducer.

The rectal wall distance (RWD) is the distance from the transducer to the rectal wall. The RWD should be greater than or equal to 0.8 cm. If the distance between the rectal wall and the transducer is close to its upper limit (2.0 cm for the 4.0 cm transducer; 2.3 cm for the 3.0 cm transducer), a yellow warning appears on the image. If the RWD exceeds its upper limit, a red appears on the image, and an alarm will pause the therapy.

The physician adjusts the dosage (power) depending on the RWD, tissue response, near field changes, movement or swelling, and Reflectivity Index Monitor value. Once treatment is initiated, the treatment pulses are automatically delivered according to the treatment plan. A physician can skip the HIFU pulse if the treatment zone for that particular cycle is outside the prostate capsule or in a region that the physician does not want to treat. A physician can pause or stop a treatment.

The real-time imaging feature also intends to allow the physician to recognize the instability of the water level on the monitor. The rectal wall image on the monitor sags outside of the planned treatment area for a slow leak. If a rupture occurs during insertion of the probe into the subject, the image showing the area between the transducer and rectal wall (minimum of 0.5cm) fall flats. In either situation, the Emergency stop button should be depressed to stop treatment (if the probe is actively firing), the probe should be immediately withdrawn from the patient. After the treatment, the patient will have a suprapubic catheter for 2-4 weeks post-HIFU.

5.4 Safety Features

The system incorporates a variety of safety features to reduce the likelihood of non-target tissue (particularly the rectal wall, the bladder, and the external urinary sphincter) from being heated to therapeutic levels. Below is a listing of important features that are unique to this device:

- Emergency Stop Button
- Automatic System Check prior to therapy
- Temperature monitor: automatic pause of therapy if levels exceed safety limits
- Imaging: if image does not arrive when expected, transducer movement is stopped
- Tissue reflectivity: software examines the “live” linear images taken during the course of a treatment; a Reflectivity Index Measurement is monitored to detect cavitation near the rectal wall
- Rectal wall distance: automatic termination of the treatment if the distance to the rectal wall location is >2.0 cm for the 4.0 cm transducer, or > 2.3 cm for the 3.0 cm transducer

- Reverberation: software monitors the estimated rectal wall location for suspected ultrasound blockage (reverberations on the image)
- Independent Watchdog Timer Circuitry
- Cooling water temperature: automatic termination of the treatment if the temperature exceeds 30°C
- Forward/Reverse RF Power Sensing: monitors maximum power of RF amplifier
- Transducer Open/Short circuit detection
- HIFU ON/OFF cycle monitoring

5.5 Device Modifications

Since the approval of IDE G080057 for the clinical investigation of this device, several device modifications have occurred. SonaCare notified FDA of these changes and sought approval, when necessary, through the submission of supplements to the IDE. These device modifications are summarized in the PMA, and include minor updates to the system design, software, and manufacturing. The applicant concludes that none of these changes impacts the ability to use the clinical and performance data from the IDE to support the final version of the device, which is the subject of this PMA.

FDA Comment: ***None of the changes made during the IDE impact the HIFU output or other critical treatment parameters. The changes are minor upgrades/enhancements to modernize the system, replace obsolete components, improve manufacturability, or correct technical problems, which either are not apparent to the user or have no change to the device's clinical use. While several of these changes included new or improved safety features, none invalidate the ability to use the data from the IDE version of the system in evaluating the safety and effectiveness of the PMA version proposed for approval.***

Since the submission of the PMA, a major design change occurred to the Sonachill to change the path of water being circulated through the probe (for cooling) from a single to a dual loop. This change was implemented to address concerns about the inability to clean the water path, and potential cross contamination of the water path and probe between patients. There was no change to the probe design or the user interaction with the probe at the time of treatment.

FDA Comment: ***Functional testing of the Sonachill was performed to ensure the change of the water path loop does not impact the ability of the Sonachill to circulate water via a water path through the probe and to cool the rectal wall and HIFU transducer. This change did not impact the HIFU output or other critical treatment parameters and therefore does not***

invalidate the use of the data from the IDE to evaluate the safety and effectiveness of the version proposed for PMA approval.

Although the pre-clinical and clinical studies were conducted on earlier versions of the device, assessment of the device changes indicates that these studies can be used to support the PMA device.

6. Pre-Clinical Studies

6.1 Performance Testing and Characterization

A series of bench and animal studies were performed to characterize the performance of the Sonablate 450 device. The specific tests included are as follows:

Simulation studies: computer modeling of lesion geometry and temperature profile

- The results of these computer simulations were used to show the Sonablate transducer acoustic focal zone field intensity. The temperature rise and thermal intensity was modeled and showed the predicted lesion size/location. The treatment parameters used in these studies were equivalent to the current device (3 seconds ON and 6 seconds OFF cycle). This testing was used to support initiation of the G060129 clinical study.

In vitro studies: evaluation of lesion geometry in turkey tissue

- Lesion characteristics were studied in 7 turkey tissues.

In vivo studies: evaluation of lesion geometry in canines and temperature of non-target tissue

- A study of 5 dogs was conducted to evaluate the performance of the device, including the ability to control the delivery of HIFU, produce coagulative necrosis in targeted tissue, and maintain surrounding (non-targeted) tissue and rectal wall temperature. The prostate was ablated in a specific focal zone using the HIFU probe. There was no evidence of rectal wall injury or damage, or ablation outside of the planned treatment zones. The rectal wall (and probe tip temperature) remained below 20°C during the entire treatment, verifying the cooling capacity of the active chiller system and its ability to maintain the rectal wall temperature. Targeted tissue was ablated and necrosed, with temperatures up to 100°C measured in the focal zone of the transducer, while intervening and surrounding tissue temperature was maintained at 37°C.

- An additional canine study was performed to observe the prostate vascular blood flow in four dogs and evaluate the effect on the rectal wall after HIFU. The histology report states that all rectal tissue had vascular congestion, which is non-specific and clinically insignificant. There was no histologic evidence of rectal mucosal damage. The prostatic parenchyma showed extensive damage (apoptosis) and coagulative necrosis. The capsule tissue was intact.

The PMA summarizes the results of characterization and calibration tests performed on the Sonablate 450. Specifically, the following technical parameters were measured and verified in this testing: acoustic power output, focal site intensity, prostate volume being treated, average temperature outside the treatment volume, and ultrasound imaging functionality.

FDA Comment: FDA reviewers found this information adequate.

6.2 Biocompatibility Testing

Of the patient contacting components of the Sonablate, the following are legally marketed as stand-alone devices and do not require separate biocompatibility testing: the probe sheath and ultrasound transmission gel. For the remaining components and accessories of the Sonablate that have, or could potentially have, patient contact, cytotoxicity, intracutaneous reactivity, and sensitization testing were conducted and submitted for review. The probe failed cytotoxicity testing.

FDA Comment: The failure of the cytotoxicity testing for the Sonablate rectal probe is under discussion between SonaCare and the FDA. The panel will not be asked to discuss cytotoxicity testing.

6.3 Software Validation

The Sonablate has three software applications. The main application or console software controls the treatment procedure, imaging, monitoring, interface with the display, printer, keyboard, and storing data. The motion control program controls the motors that control transducer placement. The watchdog timer controls safety measures including alarms. Software verification and validation testing for each program was submitted by the applicant.

FDA Comment: FDA reviewers found this information adequate.

6.4 Electrical Safety and Electromagnetic Compatibility Testing

The applicant has provided information on the electrical safety and electromagnetic compatibility testing performed in accordance with IEC 60601 standards.

FDA Comment: FDA reviewers found this information adequate.

6.5 Sterilization and Shelf Life Validation

The only component of the Sonablate that is provided sterile is the Procedure Treatment Kit. The probe sheath and ultrasound transmission gel are legally marketed as stand-alone devices, and are provided to SonaCare in final, packaged form with validated expiration dates. Non-disposable components of the device do not have an assigned shelf life. For components that will degrade over time, a preventative maintenance schedule is provided. The applicant provided testing supporting a shelf life of 6 months for the Procedure Treatment Kit, Sonachill Cleaning Kit, and the Probe Cleaning Kit.

FDA Comment: This information has not been found to be adequate by FDA reviewers. Issues regarding a cleaning agent and shelf life testing are under discussion between SonaCare and the FDA. These issues can likely be resolved through further testing and/or appropriate labeling. The Panel will not be asked to discuss cleaning, sterilization or shelf life testing.

6.6 Reprocessing Validation

Although the probe is covered with a new probe sheath prior to each treatment, there is still the potential for microorganisms to be transferred from the patient to the probe surface during the course of treatment or when the sheath is being removed. Therefore, the probe is labeled to be reprocessed between each use (manual cleaning, followed by sterilization). To support the safety of probe reuse, the applicant has provided the reprocessing instructions, and cleaning and sterilization validation studies.

FDA Comment: FDA reviewers found this information adequate.

7. Clinical Study

Clinical data including intermediate-term follow-up were submitted in the PMA in support of the safety and effectiveness of Sonablate.

7.1 Clinical Data

Overview

The primary clinical data submitted in support of PMA approval is from the IDE G080057 pivotal trial. Sonablate prospectively developed the protocol and statistical data plan (summarized below) for analysis.

- Design: Multicenter, non-randomized, prospective, single arm study involving 20 sites (U.S. and Canada) and 200 subjects. A two-stage group sequential design was used to evaluate the safety and effectiveness of the Sonablate 450 for the treatment of locally recurrent prostate cancer with HIFU. An interim analysis was planned after the first 100 subjects have been followed for 12 months. The applicant submitted this PMA application which is based on the interim analysis results for the first 100 patients who have completed 12 months follow-up.

- Objective: Determine the safety and effectiveness of the Sonablate using data from pre-treatment screenings, treatment records, and scheduled follow-up visits through 12 months post-treatment, then annually for 5 years.

- Inclusion Criteria:
  - men with initial presentation of organ confined recurrent prostate cancer (Stages T1c and T2 only) who have been treated with EBRT (conventional, three-dimensional conformal, or Intensity Modulated Radiation Therapy (IMRT)) or proton therapy, two or more years prior, and currently have biopsy proven local recurrence; previous radiation therapy must be a documented therapeutic dose of 60 to 81Gy or GyE (gray equivalent) for proton therapy
  - negative bone scan within 6 months prior to enrollment to rule out possibility of metastases
  - negative computerized tomography scans of the chest, abdomen, and pelvis within 6 months prior to enrollment to rule out possibility of metastases
  - age $\geq$ 40 years through $\leq$ 85 years of age
  - prostate biopsy with > 10 core biopsies demonstrating 1 or more cores positive for cancer cells, within 6 months prior to treatment; prostate volume $\leq$ 40 g (cc) (HIFU subject prostate volume will be initially calculated utilizing transrectral ultrasound (TRUS) measurements during screening and verified with the use of the Sonablate before initiating the HIFU procedure; patients with prostate volumes greater than 40 g (cc) as determined by either measurement will not be enrolled in the study)
    - AP diameter of the prostate must be < 4.0 cm

- serum PSA ≥ 0.5 ng/mL and ≤ 10 ng/mL
- > 90 days post hormone therapy usages, subjects who have had or are currently undergoing hormone therapy (GnRH agonist/antagonist) must discontinue hormone therapy and go through a 90-day washout period prior to consideration for study participation, and must remain off hormone therapy throughout the duration of the follow-up period (5 years)
- signed informed consent for the HIFU treatment through the 12 month follow-up visit (8 visits) and then through the extended follow-up period of 5 years (4 additional visits)
- life expectancy > 12 months

- Exclusion Criteria:
  - American Society of Anesthesiologists criteria of IV or higher; intra-prostatic calcifications > 1.0 cm (single or continuous grouping) on 2 or more consecutive images along the same plane by either the TRUS or Sonablate 450 measurement will not be enrolled
  - active, uncorrected bleeding disorder as determined by abnormal prothrombin time, partial thromboplastin time, or International Normalized Ratio (INR) at the time of HIFU (use institutional lab normal ranges for parameters)
  - use of coumadin or any other anticoagulant, unless anticoagulation can be temporarily reversed or stopped; active urinary tract infection; interest in future fertility
  - body weight, which would preclude proper suprapubic catheter functioning, per investigator's discretion
  - inability to visualize the prostatic tissue adequately on TRUS imaging
  - use of any 5ARI drugs within 3 months prior to enrollment such as Finasteride (Proscar) or Dutasteride (Avodart)
  - a debulking transurethral resection of the prostate is not acceptable once the screening biopsy for patient selection has been conducted
  - prior treatment for prostate cancer, other than EBRT or hormone therapy; history of urethral stent or urethral surgery (urethral dilation, urethroplasty); a Uroflow exam may be conducted at the investigator's discretion
  - prior significant rectal surgery (hemorrhoidectomy is acceptable; rectal resection/fissure repair are excluded)
  - history of inflammatory bowel disease of the rectum; history of any other malignancy treated within the last 5 years, other than squamous or basal cell skin cancer
  - functional bladder problems defined as International Prostate Symptom Score IPSS > 19; current bladder cancer, urethral stricture, or bladder neck contracture; a cystoscopy may be performed at the investigator's discretion to rule out these conditions
  - urinary tract or rectal fistula
  - rectal fibrosis/stenosis; anoscopy or proctoscopy may be performed at the investigator's discretion

- anomaly of the rectal anatomy or mucus membrane; anoscopy or proctoscopy may be performed at the investigator's discretion
- prostate seroma/abscess
- current symptomatic radiation proctitis requiring creams
- participation in other investigational studies, unless approved in writing by the study sponsor

- Enrollment Period: 2009-present

- Primary study hypotheses: H_0: $P_{LC} < 40\%$ vs. H_a: $P_{LC} \geq 40\%$, where P_{LC} is the proportion of subjects who achieved local control at Month 12. The study was designed to test whether the true local control rate at Month 12 is at least 40%.

  The applicant performed a meta-analysis of biochemical free survival rates and complications of other available salvage treatments.

- Sample size calculation: The sponsor expected the HIFU local control rate to be 70%. The expected observed success rate is to be between 56%-63% after accounting for 10% - 20% missing biopsies due to the uncomfortable nature of biopsies. A sample size of 200 would provide 90% power with a two-sided significance level of 5%. An interim analysis was planned after the first 100 subjects have been followed for 12 months. A group sequential design with Pocock stopping boundary was used to stop the study early if the efficacy is shown at the time of interim analysis and maintain the study-wise Type I error rate at a level of 0.05. A two-sided significance level of 0.0294 (i.e., one-sided significance level of 0.0147) was used at the interim and final analyses.

- Analysis method: The primary analyses required for the primary and secondary endpoints were performed on the Intent-To-Treat (ITT) study population including all subjects who met the inclusion/exclusion criteria, provided written informed consent, were enrolled, and received treatment. Additional analyses were performed on the Per Protocol (PP) study population, including subjects who met the ITT requirements, and who completed the entire 12 months of the study and had biopsy results. The hypothesis was tested using a Chi-square test. Two-sided 97.06% confidence intervals were also provided after taking into account alpha spent at the interim analysis. All missing biopsy results were imputed as failures. Missing PSA values were imputed with the last-value-carried forward method.

- Patient Population: Men with histologically confirmed, locally recurrent, organ-confined, non-metastatic prostatic adenocarcinoma two or more years following EBRT, PSA $\geq$ 0.5 ng/mL and $\leq$ 10 ng/mL, 40 to 85 years of age, and with initial staging of T1c-T2 prior to radiation, who meet the criteria for salvage treatment

- Follow-up: Study visits at 6 weeks, 3 months, 6 months, 9 months, and 12 months, and annually thereafter until 5 years post treatment.

  FDA Comment:

  The sponsor indicated that the primary analysis would be performed on the ITT patient population, although additional analysis on the per protocol patient population would also be calculated.

  Missing PSA values were imputed with the last-value-carried forward method which is reasonable since the nadir or smallest PSA value is used to determine biochemical success.

  The sponsor provided a meta-analysis of biochemical recurrence free rates of other salvage treatments in order to determine their performance goal and estimate their local control rate after treatment. The meta –analysis of other salvage treatments are challenging to interpret and subject to bias due to different patient selections, device/treatment parameter variations, extent and timing of treatment, potential retreatments, etc. Previous studies have shown a wide range of biochemical recurrence-free survival and complication rates with other salvage treatments. (See Appendix 1.)

  Performance goals are usually used in situations where the disease condition is well understood and the treatment response is highly homogeneous. If treatment response is heterogeneous (i.e., heavily dependent on certain characteristics of individual patients and/or medical practice), then using a performance goal can introduce serious bias into the effectiveness comparison.

Subject Accountability

One hundred (100) subjects enrolled at 16 sites and followed through their 12 month post-treatment interval as required for inclusion were included in the interim analysis. The ITT population has 100 subjects of which 22 subjects were excluded from the per-protocol population. All these subjects did not have biopsy results and were considered as failures in the ITT population. Among those, there were 7 subjects who completed their Month 12 visit and 15 subjects who did not have a Month 12 visit. These subjects either refused to receive the biopsy or were lost-to-follow up.

Site #	Site Name	# Enrolled
13	Specialists in Urology	2
15	University of Wisconsin	5
17	New York University School of Medicine	8
18	UCLA David Geffen School of Medicine	10
20	University Hospitals Case Medical Center	1
21	Walter Reed National Military Medical Center	10
22	London Health Sciences Centre	20
24	Metropolitan Urology	6
25	Can-Am	10
26	MD Anderson Cancer Center	5
28	Urologic Consultants of SE PA	4
29	Tulane University	3
30	Fox Chase Cancer Center	8
31	Indiana University	5
39	University of Cincinnati	1
42	Tower Urology	2

	All Enrolled Subjects (N=100) (ITT)
Age	Range: 53 – 83 Mean: 69.72
Race	American Indian - 0 Asian - 0 Black - 16 Hawaiian - 0 White - 76 Hispanic - 5 Other – 3
Pretreatment PSA	Range: 0.4 – 14* Mean: 4.90

* Although the criteria for study entry is a pretreatment PSA of ≥0.5 ng/mL and ≤10 ng/mL, three subjects were found to have pretreatment PSAs outside that range (0.4, 10.1, and 14 ng/mL) when the results were received from the central lab. These are reported as protocol deviations.

	Enrolled	**Completed Month 12 follow-up and included biopsy**	**Dropped or No Biopsy**	**Included in Analysis**
		Per-Protocol (PP)	No 12-month Biopsy	Intent to Treat (ITT)
Number of subjects	100	78	22	100 = 78+22

7.2 Primary Effectiveness Analysis

The primary analysis in support of Sonablate is percentage of subjects obtaining local control of prostate cancer as defined by

1. Achieving a PSA nadir of ≤ 0.5 ng/mL within 12 months of treatment, and

2. Negative prostate biopsy at 12 months.

Overall study success was pre-defined as achieving local control of prostate cancer in 40% or more of the patients. The local control of prostate cancer rate was compared to a performance goal of 40% using a Chi Square scores test.

FDA comment: The sponsor stated that the 40% performance goal is greater than the rate for absence of biochemical failure among untreated patients; therefore, the performance goal would ensure efficacy superior to no treatment.

The Panel will be asked if it is appropriate to compare the percentage of Sonablate subjects obtaining local control of prostate cancer to a performance goal, and whether a comparison to a 40% performance goal supports the effectiveness of this treatment.

At the pre-specified interim analysis conducted after 100 patients reached 12 month follow-up:

> The sponsor reported 50% of subjects (50/100, two-sided p=0.0412) achieved local control of prostate cancer based on the ITT population. (Two-sided 97.06% confidence interval = 0.39-0.61).

FDA comment: The lower bound of two-sided 97.06% confidence interval is marginally less than 40%. The study did not meet the success criteria.

The PSA level of one subject, 22-024, while achieving a nadir of ≤ 0.5ng/mL prior to 12 months reached 14.5 ng/ml at 12 months.

> If this patient is considered a failure, then 49% of subjects (49/100, two-sided p=0.0662) achieved local control of prostate cancer based on the ITT population. (Two-sided 97.06% confidence interval = 0.38-0.60).

FDA comment: The Agency recognizes this patient as a success according to the protocol success criteria. However, this patient meets the Phoenix definition of biochemical failure, which is a rise in PSA of 2.0 ng/mL or greater above the nadir .[5] Therefore, the Agency considers this patient a clinical failure. Considering this patient a failure, again, the lower bound of two-sided 97.06% confidence interval is marginally less than 40%. The study did not meet the success criteria.

Additional efficacy information was provided on 16 subjects who were enrolled through a cutoff date of January 31, 2014 (and not included in the interim analysis). Eight of 16 patients have reached the 12 month endpoint. Of these 8 patients, there were 5 failures and 3 successes.

FDA Comment:

Biochemical failure definitions:

1. ASTRO definition of biochemical failure: Defined in 1996 by the American Society of Therapeutic Radiology and Oncology (ASTRO) as three consecutive rises in PSA after the nadir.[4]

2. Phoenix definition of biochemical failure (intended to replace the 1996 ASTRO definition): Defined in 2005 by ASTRO as a rise in PSA of 2.0 ng/mL or greater above the nadir. Additionally the date of failure is to be determined "at call" (not backdated). It is recommended that investigators be allowed to use the ASTRO Consensus Definition after EBRT alone (no hormonal therapy) with strict adherence to guidelines as to "adequate follow-up." To avoid the artifacts resulting from short follow-up, the reported date of control should be listed as 2 years short of the median follow-up. For example, if the median follow-up is 5 years, control rates at 3 years should be cited. Retaining a strict version of the ASTRO definition would allow comparisons with a large existing body of literature.[5]

The IDE study currently meets the definition for time to follow-up as defined by the Phoenix criteria, because control rates are reported at 1 year, and the median follow-up is currently between 3 and 4 years.

The panel will be asked to discuss whether local control of prostate cancer for individual subjects can be defined as

1. ***achieving a PSA nadir of ≤ 0.5 ng/mL within 12 months of treatment***
2. ***and negative biopsy at 12 months.***

The panel will be asked to discuss whether the clinical data supports the effectiveness of this new treatment.

7.3 Secondary Effectiveness Analysis

The analyses of secondary endpoints were performed on the ITT population without formal statistical tests.

1. Mean change in the International Index of Erectile Function (IIEF-5) score

   The International Index of Erectile Function (IIEF-5) score is a sexual health inventory for men to diagnose the presence and severity of erectile dysfunction. It includes five items, which were selected based on ability to identify the presence or absence of erectile dysfunction and on adherence to the National Institute of Health's definition of erectile dysfunction, focusing on erectile function and intercourse satisfaction.

IIEF-5 score (scores range from 5-25): Low values correspond to severe erectile dysfunction and high values correspond to limited erectile dysfunction. Potency is defined by an IIEF score of 12 or more. There are 97 patients in the ITT population. Among 45/97 subjects with potency at baseline (46.4%), 10/45 (22%) of them retained potency at Month 12, while 2 out of 52 impotent patients at baseline achieved potency at Month 12.

Potency information among 100 patients who were included in the interim analysis

	12 months follow-up			
Baseline	Not evaluated	impotent	potent	Total
Not evaluated	3	0	0	3
impotent	10	40	2	52
potent	6	29	10	45
Total	19	69	12*	100

*A total of 13 patients were potent at 12 months (IIEF score of 12 or greater), however, one of these subjects (30-017) is not included in the first 100 subjects.

FDA Comment:

The rate of erectile dysfunction after treatment with the Sonablate was 88% according to IIEF-5 scores. Previous studies of alternate salvage treatments including radical prostatectomy, robot assisted radical prostatectomy, cryotherapy, and brachytherapy have erectile dysfunction rates that range from 61-100%.[6] The rate of erectile dysfunction after

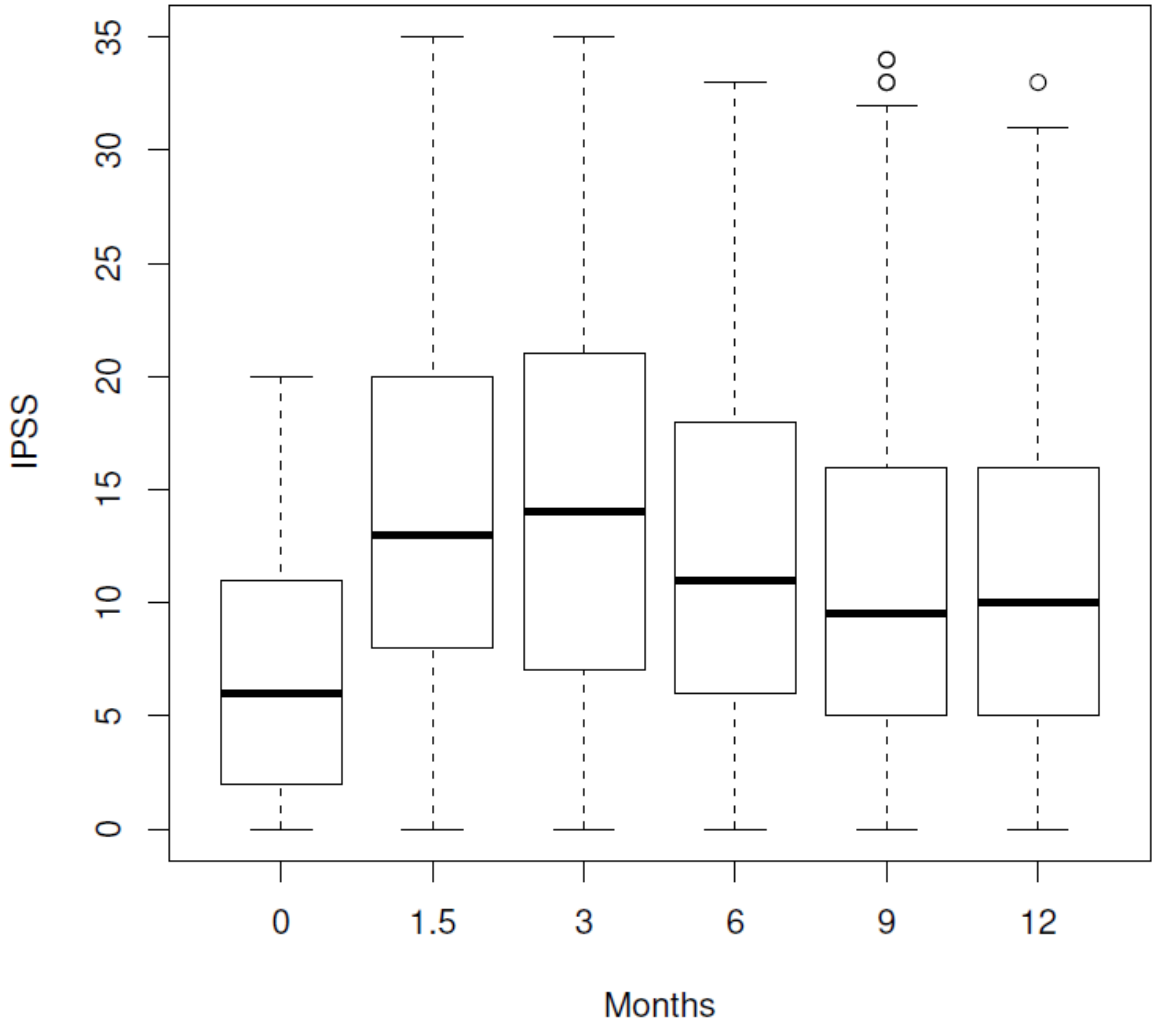
treatment with the Sonablate seems to be in the range of those seen after other salvage therapies.

2. Mean change in the IPSS score

   The International Prostate Symptom score is a symptom index that includes 7 topics including frequency, nocturia, weak urinary stream, hesitancy, intermittence, incomplete emptying and urgency.

   IPSS (scores range from 0 to 35): High values in IPSS correspond to severe symptoms. There are 98 patients in the ITT population. There is a 3.5 point median increase over baseline at 12 months with a 97.06% confidence interval of (2.00, 6.00).

Boxplots of IPSS Scores by Time of Visit



FDA Comment: ***An increase in IPSS scores is not uncommon in salvage treatments.***

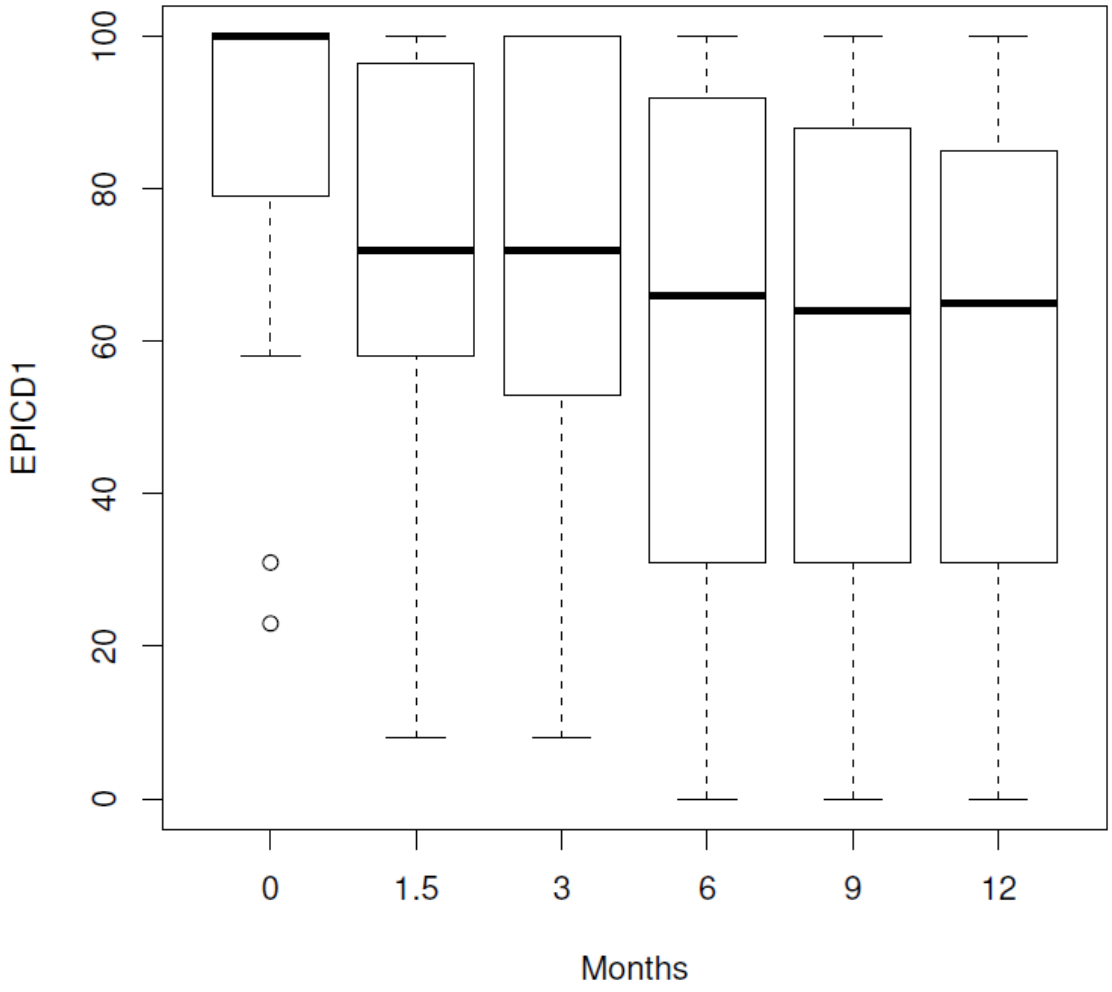
3. Mean changes in the Expanded Prostate Cancer Index Composite (EPIC-26) values

   The Expanded Prostate cancer Index Composite (EPIC) is a health related quality of life questionnaire used to evaluate patient function after prostate cancer treatment. The six domain scores are standardized between 0 and 100, and high scores are better than low scores.

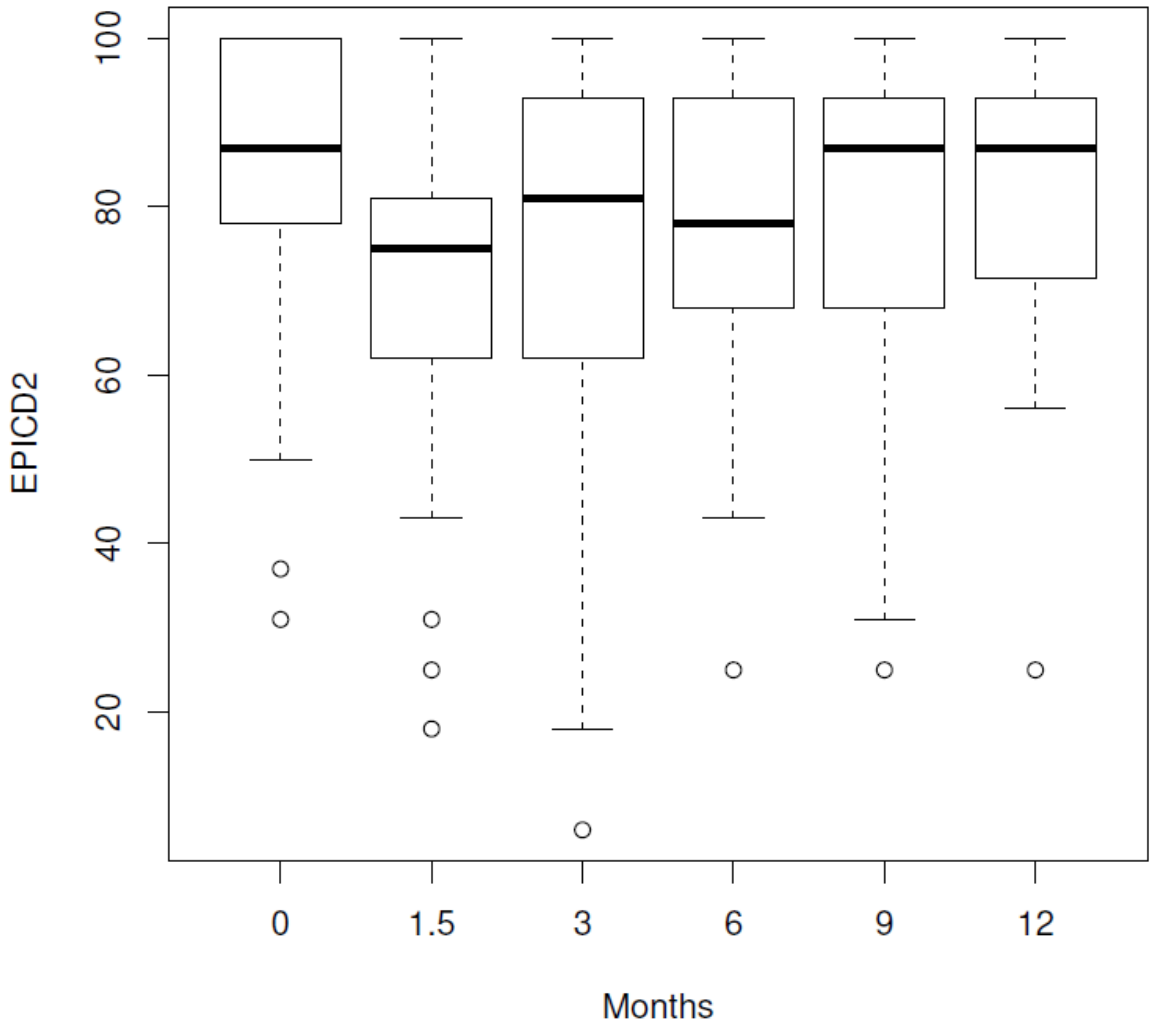
   EPIC-26 (scores range from 0-100 with six domains) The EPIC questionnaire was added to the study after 49 subjects had started. Higher scores are better than low scores. There are 44 subjects in the ITT population. Three areas (Urinary Incontinence, Urinary Function, Sexual Function) showed a drop post HIFU and although the other three areas (Urinary

Irritative/Obstructive, Bowel, Hormonal) showed an initial drop, they returned to very near baseline by Month 12.

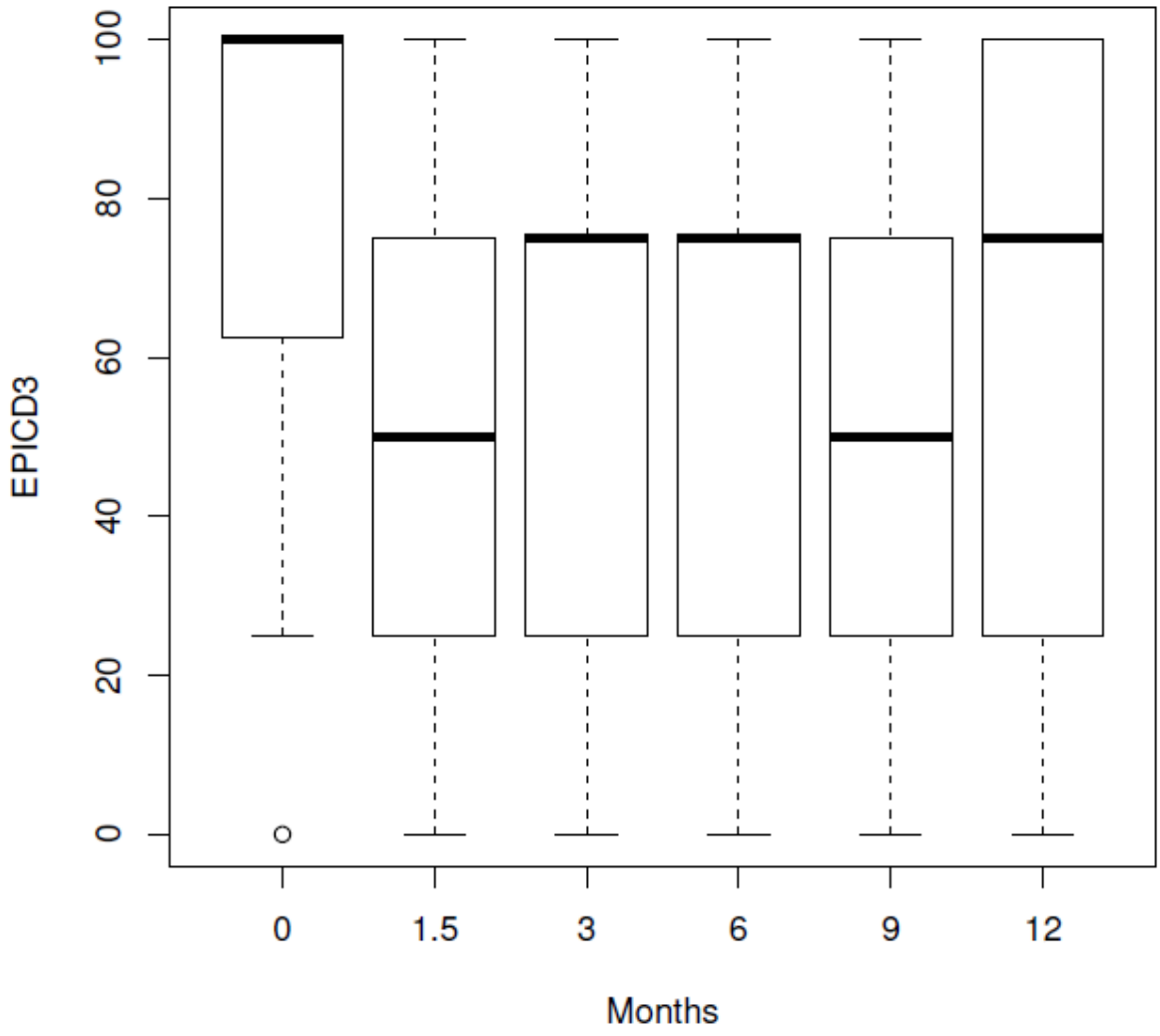
EPIC-26 Domain D1 (EPICD1): Urinary Incontinence
Boxplots of EPICD1 Scores by Time of Visit



EPIC-26 Domain D2 (EPICD2): Urinary Irritative/Obstructive
Boxplots of EPICD2 Scores by Time of Visit

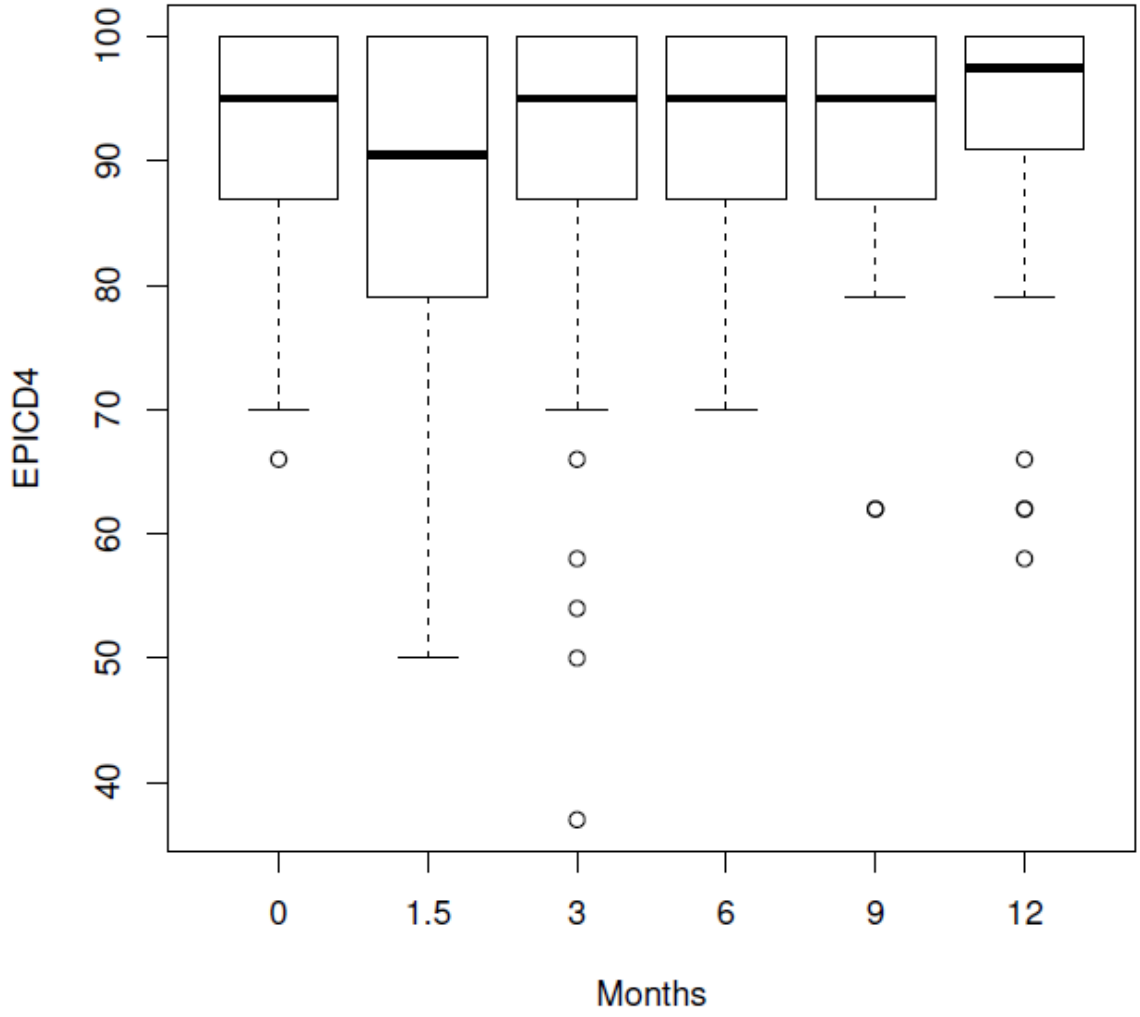


EPIC-26 Domain D3 (EPICD3): Overall Urinary Function
Boxplots of EPICD3 Scores by Time of Visit

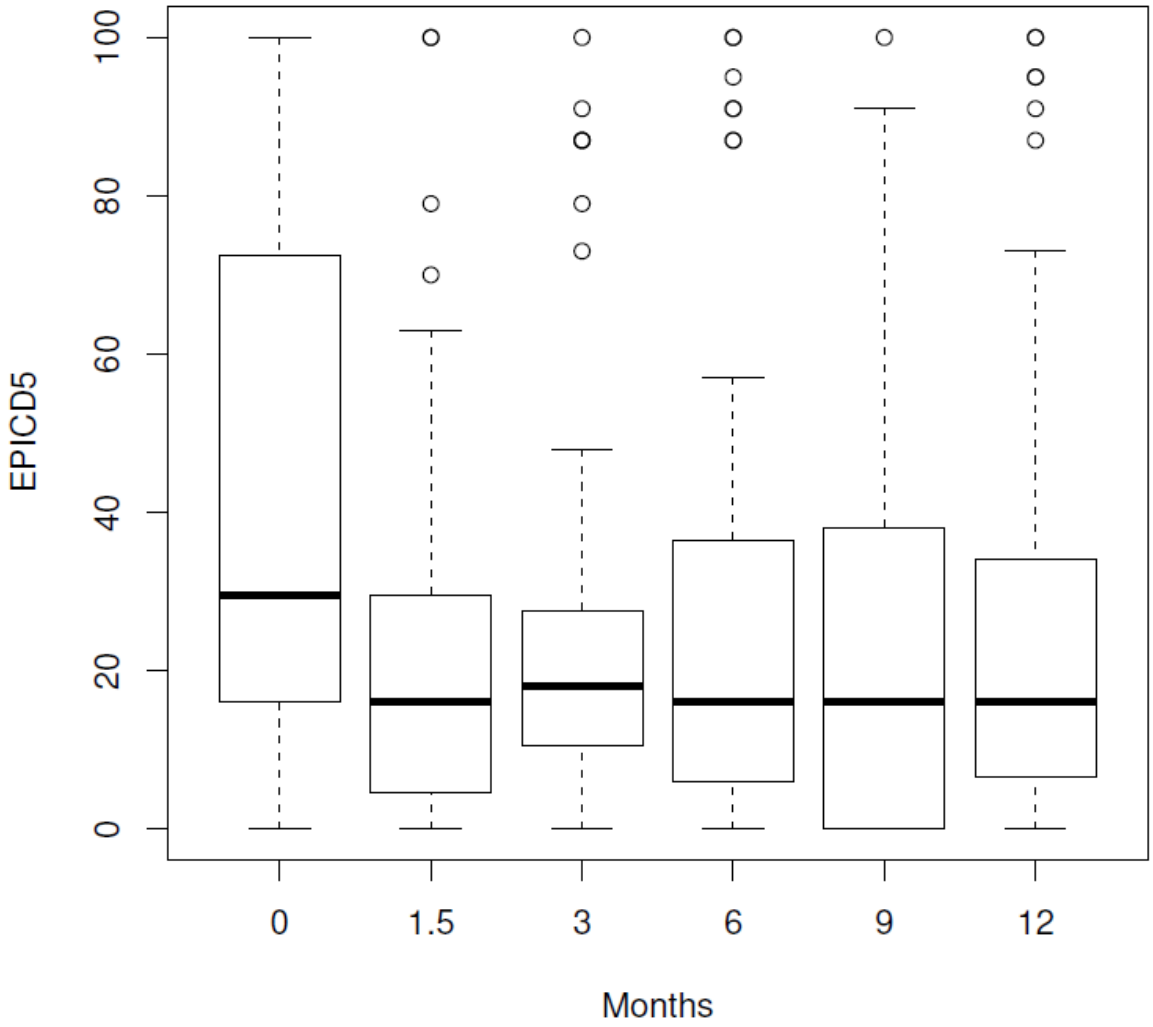


EPIC-26 Domain D4 (EPICD4): Bowel

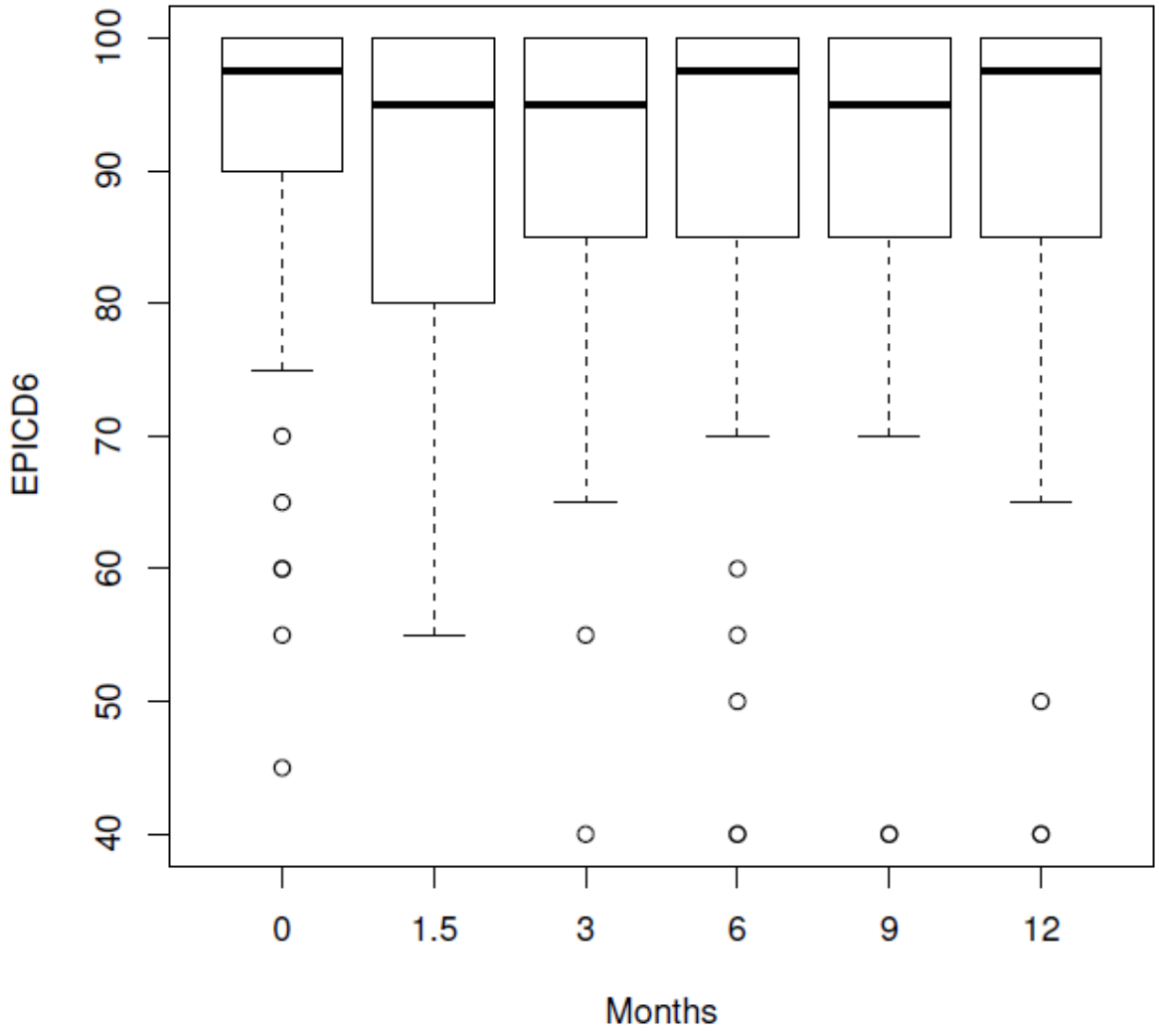
Boxplots of EPICD4 Scores by Time of Visit



EPIC-26 Domain D5 (EPICD5): Sexual Function
Boxplots of EPICD5 Scores by Time of Visit



EPIC-26 Domain D6 (EPICD6): Hormonal
Boxplots of EPICD6 Scores by Time of Visit



EPIC-26 Data (D1,D2, D5)						
	Baseline		Month 12		Paired difference = Baseline-Month12	
	Mean (SD)	Median	Mean (SD)	Median	Median	97.06% Wilcoxon CI
D1: Urinary incontinence	88.75(18.35)	100	58(31.76)	65	24	(26, 48)
D2: Urinary Irritative /Obstructive	84.45(16.58)	87	82.59(15.85)	87	0	(-6.5, 9.5)
D5: Sexual Function	41.18(32.68)	29.5	29.82(31.6)	16	8	(0, 25.5)

***FDA Comment*: Since the EPIC-26 evaluation was added after 49 subjects had started the study, the results should be used with caution.**

4. Overall and cause specific survival rates

   Survival Analysis: Two subjects died during their follow-up interval, though neither was attributed to Sonablate treatment. These subjects will be discussed further in the section, Safety Analysis, below. Based on the Kaplan-Meier function, the estimate of one year survival probability is 0.979 with a standard error of 0.015. The 95% confidence interval is (0.95, 1).

Exploratory Effectiveness Analyses:

- Sexual Aid Use

  There was no substantial observed change in the number of sexual aid medications and/or devices at baseline, compared to each follow-up interval through Month 12.

Study Period	Medications				Devices	
	Cialis	Levitra	Viagra	Other	Vacum Pump	Injection Therapy
Pre-treatment	4	1	8		1	
Week 6	1	1	3		1	
Month 3	5	3	4		2	
Month 6	1	2	5		1	
Month 9	5	1	8	2	2	1
Month 12	2	1	7	1	3	1

7.4 Safety Analysis

To evaluate the safety of the Sonablate 450, adverse events were enumerated by type, severity, frequency, relationship to study, and resolution. Adverse events were classified by Common Terminology for Clinical Adverse Events (CTCAE) class (including Renal and Urinary Disorders, Infections and Infestations, Cardiac Disorders, Gastrointestinal Disorders, General Disorders and Administrative Site Conditions, Musculoskeletal and Connective Tissue Disorders, Nervous System Disorders, and Respiratory, Thoracic, and Mediastinal Disorders.) A grade of 1 through 5 was assigned for each adverse event corresponding to mild, moderate, severe, life-threatening or disabling, and death related.

Additionally, Serious Adverse Events were defined as an event occurring while the subject is actively participating in the study that results in any of the following outcomes:

(1) death,
(2) life-threatening event,
(3) inpatient hospitalization,
(4) extension of existing hospitalization,
(5) a persistent or significant disability/incapacity, or
(6) a congenital anomaly

It is important to distinguish between the terms "serious" and "severe." The term "serious" is used with the definition above and categorizes events (i.e., they either meet the definition for serious or they do not). The term "severe" refers to the intensity of the event and can be used with any event, without regard to whether or not it meets the criteria for being classified as "serious." For example, a subject can have a severe headache, but it is not a serious event.

- Safety Results – Adverse Events:
  - A total of 766 adverse events were reported in 91/100 subjects.

Serious Adverse Events in the 100 patient ITT population			
	Subjects with event (n)	Subjects with event (%) [(n/100)*100]	Total events reported
Device Related	14	14%	20
Unknown relatedness	1	1%	1
Device unrelated	11	11%	14
Total Serious Adverse events	27	27%	35

  - Two serious adverse events resulted in deaths (aspiration and a cessation of life that cannot be attributed to a CTCAE term associated with Grade 5), but were determined to be device unrelated.
  - The following tables summarize all adverse events occurring in subjects classified as:

    1. Infections and Infestations,
    2. Renal and Urinary Disorders, and
    3. Gastrointestinal Disorders.

CTCAE Class: Infections and Infestations – Categories (Adverse Events for All Subjects, N=100)

CTCAE Category	Number of Subjects with event *(n)*	Percent of subjects with even *(n/100)*100*	Intensity of event				Total events reported
			Mild	Moderate	Severe	Life threatening or death	
Bacteremia	1	1	0	0	1	0	1
Bladder Infection	1	1	0	1	0	0	1
Bone Infection	3	3	0	0	3	0	3
Catheter Related Infection	6	6	0	6	2	0	8
Clostridium difficile	1	1	0	1	0	0	1
Cold and Flu Symptoms	1	1	0	1	0	0	1
Epididymitis	1	1	0	1	0	0	1
Gastrointestinal Infection	1	1	0	1	0	0	1
Lung Infection	1	1	0	1	0	0	1
Nasal infection	1	1	0	1	0	0	1
Otitis Externa	1	1	0	1	0	0	1
Penile infection	1	1	0	1	0	0	1
Prostatitis / Prostate infection	2	2	0	2	0	0	2
Scrotal Infection	6	6	0	5	1	0	6
Skin Infection	3	3	1	1	1	0	3
Upper Respiratory Infection	2	2	1	1	0	0	2
Urinary Tract Infection	48	48	1	85	4	0	90
Infections and Infestations - Totals	58	58	3	109	12	0	124

CTCAE Class: Renal and Urinary Disorders – Categories (Adverse Events for All Subjects, N=100)							
CTCAE Category	**Number of Subjects with event** *(n)*	**Percent of subjects with even** *(n/100)*100*	**Intensity of event**				**Total events re-ported**
			Mild	**Moderate**	**Severe**	**Life threaten-ing or death**	
Abnormal Urinalysis	1	1	1	0	0	0	1
Benign Prostatic Hyperplasia	1	1	1	0	0	0	1
Bladder Neck Contracture	5	5	0	5	0	0	5
Bladder Neck/Urethral Stricture	8	8	0	7	2	0	9
Bladder Spasm	15	15	2	15	0	0	17
Bladder Stones	2	2	0	0	2	0	2
Bruised Kidney	1	1	1	0	0	0	1
Chronic Kidney Disease	1	1	1	0	0	0	1
Cystitis Noninfective	4	4	2	2	0	0	4
Dislodged S/P Catheter	1	1	1	0	0	0	1
Dysuria	2	2	2	0	0	0	2
Hematuria	48	48	44	14	5	0	63
Incompetent Sphincter	1	1	1	0	0	0	1
Inconsistant Stream	1	1	1	0	0	0	1
Nocturia	1	1	0	1	0	0	1
Odor to Urine	1	1	1	0	0	0	1
Penile Discharge	1	1	1	0	0	0	1
Pyuria	1	1	1	0	0	0	1
Renal Calculi	1	1	0	0	1	0	1
Renal Colic	1	1	0	1	0	0	1
Urinary Fistula	3	3	0	0	3	0	3
Urinary Frequency	37	37	12	28	0	0	40
Urinary Incontinence	44	44	22	29	4	0	55
Urinary Retention	47	47	3	65	5	0	73
Urinary Tract Obstruction	18	18	6	11	3	0	20
Urinary Tract Pain	18	18	7	14	0	0	21
Urinary Urgency	26	26	7	19	0	0	26
Urine Cytology	1	1	0	1	0	0	1
Weak Urinary Stream	2	2	1	1	0	0	2
Renal and Urinary Disorders - Totals	88	88	118	213	25	0	356

CTCAE Class: Gastrointestinal Disorders -Categories (Adverse Events for All Subjects, N=100)

CTCAE Class	Number of subjects with event *(n)*	Percent of subjects with event *(n/100)*100*	Intensity of event				Total events re-ported
			Mild	Moderate	Severe	Life threaten-ing or death	
Abdominal Pain	3	3	0	3	0	0	3
Anal Pain	9	9	6	4	0	0	10
Chipped Tooth	1	1	0	1	0	0	1
Colon polyp	1	1	1	0	0	0	1
Constipation	20	20	8	12	0	0	20
Dental Caries	1	1	0	1	0	0	1
Diarrhea	7	7	7	1	0	0	8
Diverticulitis	1	1	0	1	0	0	1
Dry Mouth	1	1	1	0	0	0	1
Dyspepsia	2	2	1	1	0	0	2
Fecal Incontinence	3	3	2	1	0	0	3
Flatulence	2	2	1	1	0	0	2
Gastric reflux	1	1	0	1	0	0	1
Hematochezia	1	1	1	0	0	0	1
Hemorrhoids	2	2	2	0	0	0	2
Lower Gastrointestinal Hemorrhage	3	3	1	1	1	0	3
Nausea	2	2	1	1	0	0	2
Oral Pain	1	1	0	1	0	0	1
Positive Fecal Leukocytes	1	1	0	1	0	0	1
Rectal Fistula	5	5	0	3	4	0	7
Rectal Hemorrhage	1	1	1	0	0	0	1
Rectal Mucositis	1	1	1	0	0	0	1
Rectal Pain	4	4	3	1	0	0	4
Rectal polyp	2	2	1	1	0	0	2
Small Intestinal Obstruction	1	1	0	0	1	0	1
Stomach Pain	2	2	1	1	0	0	2
Vomiting	5	5	2	3	0	0	5
Gastrointestinal Disorders - Totals	45	45	41	40	6	0	87

FDA Comment:

The most concerning adverse events are rectal fistulas. There were 7 rectal fistulas adverse events in 5 patients resulting in a 5% rectal fistulas adverse event rate after treatment with the Sonablate. Four rectal fistula events were Grade 3 and two rectal fistula events were Grade 2. Three patients required medical management and 2 patients required surgical treatment. Previous studies of alternate salvage treatments including radical prostatectomy, robot assisted radical prostatectomy, cryotherapy, and brachytherapy have rates of rectal fistula that range from 0-29%.[7] The rate of rectal fistulas after treatment with the Sonablate seems to be in the range of those seen after other salvage therapies.

Urinary incontinence after treatment with the Sonablate was reported 55 times in 44 patients resulting in a 44% urinary incontinence rate. Previous studies of alternate salvage treatments including radical prostatectomy, robot assisted radical prostatectomy, cryotherapy, and brachytherapy have greatly varied rates of urinary incontinence ranging from 10-72%.[8, 9] The rate of urinary incontinence after treatment with the Sonablate seems to be in the range of those seen after other salvage therapies. See Appendix 1 for additional information on previous studies.

Note that erectile dysfunction is discussed under the secondary endpoint analysis.

FDA reviewers found the safety information to be adequate.

Physician Training:

In April 2011, based on an interim review of the safety profile initiated by the sponsor for the Sonablate treatments, all clinical proctors were retrained using an updated Physician's Instruction Manual and each clinical investigator was then trained by a clinical proctor to improve their technique. In addition, an experienced HIFU Proctor was added to the treatment team for all clinical trial cases conducted. There are 61 subjects in the pre-training group and 39 in the post-training group. An analysis was done to determine if the safety profile was impacted by retraining. There is no significant difference between the adverse event rate pre and post training.

	Pre Training (n=61 patients)	Post training (n=39 patients)
Infections and Infestations		
Patients with ≥ 1 Adverse Event	33/61 = 54.1%	25/39 = 64.1%
Patients with No Adverse events	28/61 = 45.9%	14/39 = 35.9%
Renal and Urinary		
Patients with ≥ 1 Adverse Event	52/61 = 85.2%	36/39 = 92.3%
Patients with No Adverse events	9/61 = 14.8%	3/39 = 7.7%

FDA Comment:
Since there was no statistically significant decrease in adverse event rates after clinician training, the Agency noted that physician training was not effective in decreasing the rate of adverse events.

In the study protocol, the sponsor stated that the study would be reviewed for potential stoppage or modification if a rectal fistula rate was determined to be greater than 3%. At the interim analysis, the rate of rectal fistulas was 5%.

It is unclear whether further physician training should be explored and required. While the adverse event rates seem to be similar to other salvage therapies, it is unclear if different methods of training may be able to decrease the adverse event rate.

Additional safety information on an additional 16 patients enrolled after the interim analysis (through a cutoff date of January 31, 2014) was provided.

Adverse Events of 116 Patients:

A total of 879 adverse events were reported in 111/116 subjects.

Serious Adverse Events in the 116 patient population			
	Subjects with event (n)	Subjects with event (%) [(n/116)*100]	Total events reported
Device Related	19	16.4 %	25
Unknown relatedness	1	0.9 %	1
Device unrelated	13	11.2 %	16
Total Serious Adverse events	30	25.9 %	42

- o One serious adverse event (life threatening) was a catheter related infection but the patient recovered.
- o Two serious adverse events resulted in deaths (aspiration and a cessation of life that cannot be attributed to a CTCAE term associated with Grade 5). These events were identified in the interim analysis of 100 patients, but determined to be unrelated to the device.

The sponsor provided specific information about rectal fistula rates before and after physician training.

Serious Rectal Fistula Rate Pre and Post Physician Training (n=116)		
	Pre-Training Program	Post-Training Program
Medical Management	3	0
Surgical Management	1	1
Subjects treated	61	55
Fistula rate	4/61 (6.6%)	1/55 (1.8%)

FDA Comment:
Although there was no statistically significant decrease in the rate of rectal fistulas after clinician training, there is a decreasing trend in the fistulas rate after the retraining program.

As stated previously, it is unclear whether further physician training should be explored and required. While the rectal fistula rates seem to be similar to the rates of rectal injury after other salvage therapies, it is unclear if different methods of training may be able to decrease the rectal fistula rate.

Power Level:
The user of the Sonablate 450 is required to adjust the power level based on echogenic changes in the linear image during treatment. The echogenic changes are of two kinds:

1) boiling or "popcorn" and
2) microbubble "clouds."

Popcorn Grade	**Popcorn Definition**
Grade 1	Small, non-overlapping hyperechoic regions contained within the treatment zone
Grade 2	Contiguous hyperechoic regions (connecting to adjacent treatment sites) within the treatment zone
Grade 3	Large hyperechoic regions or microbubble clouds appearing outside the treatment zone

The sponsor reported the relationship between Popcorn Grades and Serious Adverse Events.

Two subjects did not have popcorn values. The rates of serious adverse events are similar in patients with Grade 3 popcorn and Grade 1 or 2 popcorn. 26.3% (i.e., 5/19) serious adverse events occurred in patients with Grade 3 popcorn. 24% (i.e., 19/79) serious adverse events occurred in patients with Grade 1 or 2 popcorn.

The primary effectiveness endpoint, local control, is also summarized by popcorn grade. Among 19 patients with Grade 3 popcorn, 14 (73.7%) patients achieved local control. Patients with Grade 1 or 2 popcorn appear to have lower control rate. Thirty-four (34) out of 79 (43%) patients with Grade 1 or 2 popcorn achieved local control.

***FDA Comment*: FDA reviewers agree that greater effectiveness is shown with Grade 3 popcorn values. FDA reviewers also agree that it appears that Grade 3 popcorn values do not incur more adverse events than Grade 1 or 2 popcorn values.**

Probe Sheath Tear, Breaks or Ruptures:
The sponsor provided the following definitions:

- probe sheath tear: a small puncture in the probe sheath that occurs during set-up; if the technician sees water droplet formation on the outside of the probe sheath, the sheath will be replaced prior to insertion
- break: an obvious and spontaneous opening in the probe sheath during set-up or insertion
- rupture: an immediate and spontaneous opening in the probe sheath after the probe has been inserted into the patient

Probe sheath ruptures were recorded but not originally considered as adverse events and therefore were not tracked on the Adverse Event Case Report Form. Any breaks that occurred during set-up or treatment were noted on the technician's case report form.

For the 116 subjects reported, there were 10 (8.6%) subject procedures affected by a probe sheath break or rupture. Two (2) of these subject procedures had two (2) incidences each during the same case, for a total of 12 instances of disruption in probe sheath integrity.

9 probe sheath breaks occurred during procedure set-up:

- 1 break during set-up by the technician when water was added to the sheath
- 8 breaks occurred during probe insertion by the physician and manipulation of probe into the rectum but prior to successful insertion of the probe into the rectum

3 probe sheath ruptures occurred during HIFU treatment while the probe was within the rectum:

- 1 rupture occurred when additional water was added to the sheath
- 2 ruptures occurred during treatment

FDA Comment:
FDA reviewers found the information about probe sheath tears to be adequate.

Adverse Events per Site**:**
One site has a disproportionate number of adverse events, both serious/severe and overall,. The sponsor attributed the number of adverse events at this site to be due to staff who intervened surgically much earlier in the patients' care than any other sites. The physician training and the Physician's Instruction Manual recommend conservative medical management to allow the post-radiation/post-HIFU tissue to heal. The sponsor recommends allowing the tissue to heal by treating urinary retention/incontinence medically with a urinary catheter and antibiotics (if needed) for a period up to one year before initiating corrective surgical treatment.
Each of the four subjects treated at this site had surgical intervention within 90 days of treatment. Two of the four had multiple interventions (suprapubic catheter placement, transurethral resection of the prostate, and/or cystoscopy) within six months of treatment; these subjects have ongoing urinary AE's (28-002 = incontinence, urinary fistula, urethral stricture, urinary frequency, urinary tract infections; 28-014 = incontinence, bladder neck contracture).

The sponsor met with this site several times and asked that they revise their follow-up plan with their subjects.

The panel will be asked discuss whether the clinical data provides reasonable assurance that the proposed device is safe.

7.5 Subgroup Analysis

Subgroup analyses were performed for race.

Local Control by Race – Observed Frequencies (n=100)				
	Black or African American	White	Hispanic	Other
Yes	10/16 (62.5%)	35/76 (46.1%)	5/5 (100%)	0/3 (0%)

7.6 Protocol Deviations

The sponsor provided a summary of protocol deviations.

Protocol Deviations	
Missed Test, procedure or visit	191
Failure to follow protocol	43
Device Failure	5
Visit outside study window*	135
Did not meet inclusion/ exclusion criteria	34
Total	408

* When evaluating visits based on 30 days +/- visit date, instead of a 5-day (6-week visit), 7-day (3-month visit), or 14-day (6- and 9-month visits) window, only ten (10) are outside of window.

Inclusion and Exclusion Criteria Deviations	
Subject Did not Meet I/E Criteria	**N**
Bone Scan not within 3 months of treatment (prior to V6 protocol approval)	1
CT scan not done	15
IPSS > 19	1
Testosterone Level Out of Range (prior to V5 protocol approval)	2
Age >80 (prior to V5 of protocol approval)	1
Subject did not have "clinical stages T1c and T2a only" (prior to V5 of protocol approval)	4
PSA < 0.5ng/mL or >10ng/mL	3
Biopsy <10 cores	2
Biopsy >6months	1
EBRT dosage not within Protocol Range 60-81Gy	3
Current urethral stricture at time of treatment	1
Total	34

The most common reason for a subject to not meet inclusion criteria is that the CT scan was not done during the screening visit. This was a decision made by the radiologists. Although a CT scan was ordered, it is not a standard of care procedure for a prostate cancer evaluation; so on 15 occasions, the order for the CT scan of the chest was converted to a chest x-ray without contacting the urology research staff.

***FDA comment*: The missed tests or procedures were addressed in the analysis by using the last value carried forward. The most concerning protocol deviations were to inclusion and exclusion criteria. Of those, the most concerning criteria are the PSA values outside the accepted range (3) and a biopsy at greater than 6 months (1).**

Missing Biopsies

As of January 31, 2014, 27 (n=116) subjects have missing biopsy results.

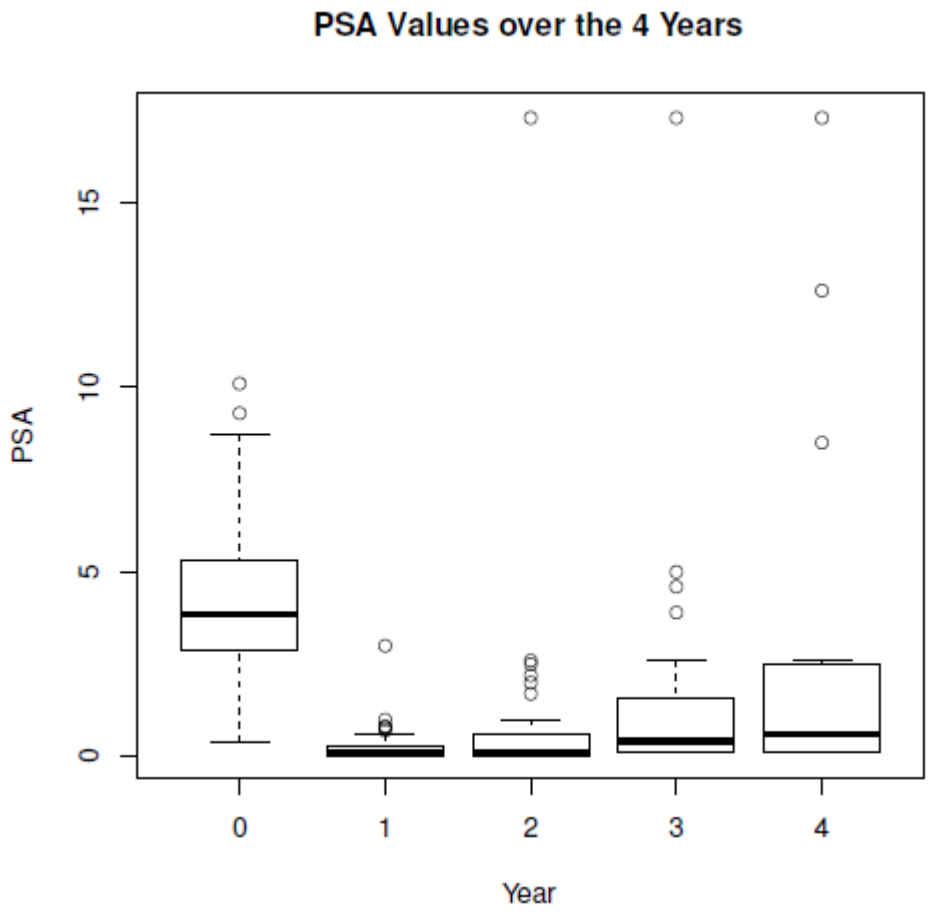
Reasons for missing biopsy	Met nadir (N=13)	Did not meet nadir (N=14)
Death (not related to study)	1	1
Disease progression	0	7
Investigator decision (other health reason prevented biopsy)	2	1
Subject withdrew consent	10	5

FDA Comment:
The sponsor indicated that many missing biopsies were due to patients declining to have the biopsy performed. Patients with missing biopsies were considered failures.

7.7 Long Term Follow-up

Among the 100 subjects included in the interim analysis, 43 out of 50 subjects who achieved local control at Month 12 have a visit beyond Month 12. One subject (b)(6) did not have a Month 12 PSA or any subsequent visit. Therefore 42 subjects had available follow-up visits at Month 12, 39 at Year 2 (i.e., 3 subjects had not completed the visit but were followed up at later visits), 26 at Year 3 (i.e., 16 subjects had not completed the visit but were followed up at later visits), and 17 at Year 4 (i.e., 25 subjects had not completed the visit but were followed up at later visits), respectively. PSA levels are summarized below by time using boxplots with last-value-carried-forward for missing values.

Number of Patients who reached long term follow-up (Patients who achieved local control n=43)					
	12 Months	Year 2	Year 3	Year 4	Year 5
n	42	39	26	17	0



Among 16 additional subjects enrolled since July 2013, no subjects had an annual visit beyond 12 months. Three (3) subjects had biopsies at Month 12 which were negative and are classified as treatment successes, per protocol, 2 subjects withdrew prior to Month 12, and 3 subjects dropped with last visit at Month 12 but did not have a final biopsy, so are all considered failures. The remaining 8 subjects are still on study.

A total of 81 out of 116 subjects completed 12 months follow-up.

8. Post-Approval Study Considerations

<u>FDA Comment</u>: The inclusion of a Post-Approval Study section in this summary should not be interpreted to mean that FDA has made a decision or is making a recommendation on the approvability of this PMA device.

If the Sonablate 450 device were to be approved, FDA believes a post-approval study would be necessary. Through review of the premarket data, the FDA review team has identified the following post-market concerns:

- Evaluation of long term outcomes associated with the device safety.
- Evaluation of long term device performance regarding effectiveness.

The applicant is proposing to conduct a PAS in which the overall goal is to generate long term clinical data from the use the Sonablate 450 device in the United States to evaluate long-term safety and efficacy of treatment with regard to biochemical failure and disease recurrence. The applicant submitted a PAS protocol interactively on July 8, 2014. An overview of the PAS is provided in the table below, followed by FDA's assessment.

8.1 Overview of Applicant's PAS Proposal

Study Component	**Description**
Study Objective	To evaluate the long-term safety and effectiveness of the HIFU treatment with the Sonablate in subjects with locally recurrent prostate cancer after failure of primary external beam radiotherapy.
Study Design	The proposed PAS is a continued follow-up of the non-randomized, prospective, single arm premarket cohort study (Pivotal Study). The study subjects already consented and will be followed through 5 years.
Study Population	Men with histologically confirmed, locally recurrent, organ-confined, non-metastatic prostatic adenocarcinoma two or more years following EBRT, PSA $\geq$ 0.5 ng/mL and $\leq$ 10 ng/mL, 40 to 85 years of age, and with initial staging of T1c-T2 prior to radiation, who meet the criteria for salvage treatment, who were enrolled in the premarket phase of the study and met primary endpoints at 12 months ("treatment successes"). Subjects that do not meet the primary study endpoints at 12 months (or are distant failures confirmed by clinical or radiological evidence post-treatment) are exited and do not continue into the PAS. The rationale is subjects that show disease progression (indicated by biochemical, local, or distant failure) will need further treatment. The primary endpoint in the PAS is to determine PSA stability and long-term cancer control. The applicant states that further treatment, including hormones, would manipulate the PSA value and skew the PSA data; therefore, the applicant proposed that these subjects are not followed in the PAS.

<table>
<tr><th>Study Component</th><th>Description</th></tr>
<tr><td>Sample Size (Patients and Sites)</td><td>The Sponsor expects that 100 of the original 200 subjects will qualify for the PAS (in 20 sites). Sample size and study power calculations are based on a comparison of the observed success rate (absence of biochemical and no positive prostate biopsy) with a performance goal. The study power is presented in the following table for several sample sizes. A 40% performance goal was selected by the sponsor to show efficacy significantly superior to no treatment.

Let p be the proportion of successes at a given time point in the study. Consider the hypotheses: H_0: $p \geq 0.40$ versus H_A: $p < 0.40$, and the level of significance at 0.05.

Table 1: Power of the test to detect the alternatives (columns) p for the given sample sizes (rows) n.
<table>
<tr><th>P</th><th>0.40</th><th>0.35</th><th>0.30</th><th>0.25</th><th>0.20</th></tr>
<tr><td>n = 100</td><td>0.04</td><td>0.23</td><td>0.63</td><td>0.93</td><td>1.00</td></tr>
<tr><td>n = 80</td><td>0.04</td><td>0.21</td><td>0.55</td><td>0.88</td><td>0.99</td></tr>
<tr><td>n = 60</td><td>0.04</td><td>0.17</td><td>0.45</td><td>0.78</td><td>0.96</td></tr>
<tr><td>n = 40</td><td>0.04</td><td>0.12</td><td>0.31</td><td>0.58</td><td>0.87</td></tr>
</table></td></tr>
<tr><td>Endpoints</td><td>Effectiveness endpoints to be evaluated annually at years 2, 3, 4, and 5 during the long-term extension are:

Effectiveness will be measured by assessing local control of prostate cancer as demonstrated by absence of biochemical failure (biochemical failure is designated by the Phoenix definition as a rise of > 2 ng/mL above the PSA nadir) and no positive prostate biopsy at 12 months.

Safety Endpoints: During the long term extension to this study, only adverse events, including serious adverse events, that are classified as related to the device or procedure (per the investigator's causality determination) are to be reported.</td></tr>
<tr><td>Evaluation Endpoints</td><td>On the yearly visits, the following exams will be performed:
Concomitant medication
Urinalysis (with urine culture if clinically indicated)
PSA (serum)

All adverse events will be evaluated at each follow-up visit.</td></tr>
<tr><td>Follow-up Visits and</td><td>Subjects will be followed annually from the 2nd year post-op for a total of 5 years after the Sonablate treatment.</td></tr>
</table>

Study Component	**Description**
Length of Follow-up	
Statistical Plan	**PAS Analysis (Years 2, 3, 4 and 5)**For each year 2, 3, 4 and 5, standard summary statistics (mean, median, standard deviation, range, 95% confidence intervals) will be used to characterize the changes in the remission rate. Pre/post changes in PSA will be examined with paired Student's t-test, Wilcoxon Signed Rank tests, and repeated measures analyses of variance. Survival (overall survival, cancer-free survival) will be summarized as 2, 3, 4 and 5 year rates, with their associated 95% confidence intervals. These events will additionally be summarized with Kaplan-Meier actuarial survival curves. The sponsor states that exploratory analyses, such as Cox regression, may be performed to examine the contribution of potential baseline risk factors to primary and secondary outcomes. **Throughout the Study** Ancillary variables will be examined and reported through the Adverse Event tracking process. Any clinically significant blood chemistry or urinalysis values are reported via the CTCAE reporting system. Study data will be analyzed using validated systems (SPSS, SAS, StatXact, and R) during the study and at the time of submission of study results to the FDA; data sets in SAS transport file or other requested formats will be made available.
Study Timeline	All study subjects will be followed for 5 years post procedure (December 2022). The expected date for final report submission is June 2023

8.2 FDA Assessment of the PAS Proposal

The applicant has proposed to extend the follow-up of the premarket cohort study for 5 years post-HIFU treatment as a PAS. The subjects that were considered to have a successful treatment who are still available for follow-up at the end of the 12 month study visits will be followed through 5 years post-treatment. Below is FDA assessment of the proposal:

1. The applicant proposed the local control of prostate cancer as an effectiveness endpoint for the PAS that will be evaluated annually at years 2, 3, 4 and 5, post procedure. The local control of prostate cancer is demonstrated by absence of biochemical failure (biochemical failure is designated by the Phoenix definition as a rise of > 2 ng/mL above the PSA nadir) and no positive prostate biopsy at 12 month. However, the proposed performance goal for treatment success is only based on the PSA level (Phoenix Criteria). Additionally, biopsy is not included in the follow-up procedures (at years 2-5) that will be required for the PAS evaluation, as outlined in the revised protocol. FDA believes prostate biopsy is an important component to evaluate local control of prostate cancer and should be included on an annual basis. Please discuss the appropriateness of the proposed effectiveness endpoint, whether you believe annual prostate biopsy should be included in the study protocol and if there are any other effectiveness endpoints that should be included in the PAS as primary or secondary.

2. The applicant proposed that only subjects that were considered to have a successful treatment and are still being followed at the end of the 12-month study visits will be included in the PAS. Although this may be acceptable for evaluating long-term device effectiveness, the treated patients who failed may have long-term adverse events that need to be evaluated, despite additional treatments. The Panel will be asked to discuss whether the patients who demonstrated treatment failure at 12-months need to be followed in the PAS to assess long-term device safety.

3. The applicant proposed a 40% success rate (Phoenix definition PSA < 2 ng/mL above the PSA nadir and a negative biopsy at 12 months) for the performance goal. However, the applicant expected the success rate for HIFU devices to be 70% and only successful patients during the first 12 months (premarket period) are included in the PAS. The applicant states that a 40% performance goal "ensures efficacy significantly superior to no treatment." Please discuss an appropriate performance goal.

4. According to the applicant, “during the long term extension to this study, only adverse events, including serious adverse events, that are classified as related to the device or

procedure (per the investigator's causality determination) are to be reported." It is important that all adverse events (including rare adverse events) be monitored in the postmarket. All adverse events should be reported and classified by type (i.e., device treatment related, procedure related, no device or procedure related). The panel will be asked to discuss the appropriateness of only reporting device or procedure related adverse events as the safety endpoints, and if there are any specific safety endpoints that need to be evaluated in the PAS.

5. Sonablate is intended for use in the treatment of localized, clinically recurrent prostate cancer after failure of primary external beam radiotherapy. Within the restrictions included in the exclusion criteria of the premarket cohort study, all prostate cancer patients that are not excluded are candidates for treatment. The sponsor conducted subgroup analysis by race, training, age, and PSA in both Intent to treat (ITT) and per protocol (PP) subjects. The sponsor reported more successes with in African American subjects than expected, while fewer successes in Caucasians than expected. According to the sponsor, "For the ITT group, as age increases, the probability of local control decreases; and as baseline PSA increases, the probability of local control decreases." Therefore, age, race, and baseline PSA level subgroup analysis is recommended for continued evaluation in the PAS because these covariates can be potential confounders or effect modifiers of treatment success. The panel will be asked to discuss the need to conduct subgroup analysis in the PAS, particularly for evaluation of long-term safety and effectiveness by race, age, and baseline PSA level.

6. The applicant proposed to test the following hypotheses regarding a performance goal of 40% ($p = 0.40$) treatment success rate: H_0: $p \geq 0.40$ versus H_A: $p < 0.40$. However, the assumption for the study is that treatment success (Phoenix definition PSA < 2 ng/mL above the PSA nadir) will be 40% or more. Therefore, the hypotheses to be tested should be H_0: $p < 0.40$ versus H_A: $p \geq 0.40$. PAS statistical details will be addressed with the sponsor, if the device is to be approved.

The panel will be asked to discuss the following aspects of the proposed PAS:

- ***a. the proposed primary effectiveness endpoint, based on absence of biochemical failure (where biochemical failure is designated by the Phoenix definition as a rise of > 2 ng/mL above the PSA nadir) and no positive prostate biopsy at 12 months, and whether there are any other effectiveness endpoints that should be included in the PAS as primary or secondary***
- ***b. whether the patients who demonstrated treatment failure at 12-months need to be***

followed in the PAS to assess long-term device safety

c. the proposed 40% success rate for the performance goal

d. the appropriateness of only reporting device or procedure related adverse events as the safety endpoints, and whether there are any specific safety endpoints that need to be evaluated in the PAS

e. whether evaluation of long-term safety and effectiveness in subgroups (by race, age, and baseline PSA) should be conducted in the PAS

f. whether there are any other concerns that need to be evaluated in the post-market setting

9. Appendix 1

Biochemical Free Survival and Complication Rates of Alternate Salvage Therapies				
	Salvage radical prostatectomy	Salvage robot-assisted surgery	Salvage cryotherapy	Salvage brachytherapy
5 year progression free rate	55 %, [10] 52 %[11]	-	73 %, [12] 56 %[11]	34 %,[13] 56 %[11]
Erectile Dysfunction	72 %, [6] 72-93 % [14]	100%,[15] 80-100%[14]	61-100 %[16]	75%,[17] 72-86%[6]
Incontinence	32-50 %,[8] 50 %[11]	20-67%[14]	10 %,[9] 72 %,[18] 16 %[11]	24 %[19] 6 %[11]
Rectal injury	2-3 %,[8] 0-29 %, [7] 2-19 %,[14] 2.4 %[11]	0-9%[14]	0-4 %, [16] 0-3 %,[11] 1.6 %[11]	4 %, [19] 3.1 %[11]

10. References

1. Edwards BK, Noone AM, Mariotto AB, et al. Annual Report to the Nation on the status of cancer, 1975-2010, featuring prevalence of comorbidity and impact on survival among persons with lung, colorectal, breast, or prostate cancer. Cancer. 2014;120: 1290-1314.
2. D'Amico AV, Whittington R, Malkowicz SB, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA. 1998;280: 969-974.
3. Rodrigues G, Warde P, Pickles T, et al. Pre-treatment risk stratification of prostate cancer patients: A critical review. Canadian Urological Association Journal. 2012;6: 121.
4. Cox JD, Grignon DJ, Kaplan RS, Parsons JT, Schellhammer PF. Consensus statement: guidelines for PSA following radiation therapy. International Journal of Radiation Oncology, Biology, Physics. 1997;37: 1035-1041.
5. Roach III M, Hanks G, Thames Jr H, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. International Journal of Radiation Oncology* Biology* Physics. 2006;65: 965-974.
6. Peters M, Moman MR, van der Poel HG, et al. Patterns of outcome and toxicity after salvage prostatectomy, salvage cryosurgery and salvage brachytherapy for prostate cancer recurrences after radiation therapy: a multi-center experience and literature review. World Journal of Urology. 2013;31: 403-409.
7. Chen BT, Wood Jr DP. Salvage prostatectomy in patients who have failed radiation therapy or cryotherapy as primary treatment for prostate cancer. Urology. 2003;62: 69-78.
8. Stephenson AJ, Eastham JA. Role of salvage radical prostatectomy for recurrent prostate cancer after radiation therapy. Journal of Clinical Oncology. 2005;23: 8198-8203.

9. Anastasiadis AG, Sachdev R, Salomon L, et al. Comparison of health-related quality of life and prostate-associated symptoms after primary and salvage cryotherapy for prostate cancer. Journal of Cancer Research and Clinical Oncology. 2003;129: 676-682.
10. Bianco Jr FJ, Scardino PT, Stephenson AJ, DiBlasio CJ, Fearn PA, Eastham JA. Long-term oncologic results of salvage radical prostatectomy for locally recurrent prostate cancer after radiotherapy. International Journal of Radiation Oncology* Biology* Physics. 2005;62: 448-453.
11. Parekh A, Graham PL, Nguyen PL. Cancer Control and Complications of Salvage Local Therapy After Failure of Radiotherapy for Prostate Cancer: A Systematic Review. Seminars in Radiation Oncology, 2013:222-234.
12. Ismail M, Ahmed S, Kastner C, Davies J. Salvage cryotherapy for recurrent prostate cancer after radiation failure: a prospective case series of the first 100 patients. BJU International. 2007;100: 760-764.
13. Grado GL, Collins JM, Kriegshauser JS, et al. Salvage brachytherapy for localized prostate cancer after radiotherapy failure. Urology. 1999;53: 2-10.
14. Chade DC, Eastham J, Graefen M, et al. Cancer control and functional outcomes of salvage radical prostatectomy for radiation-recurrent prostate cancer: a systematic review of the literature. European Urology. 2012;61: 961-971.
15. Eandi JA, Link BA, Nelson RA, et al. Robotic assisted laparoscopic salvage prostatectomy for radiation resistant prostate cancer. The Journal of Urology. 2010;183: 133-137.
16. Pisters LL, Rewcastle JC, Donnelly BJ, Lugnani FM, Katz AE, Jones JS. Salvage prostate cryoablation: initial results from the cryo on-line data registry. The Journal of Urology. 2008;180: 559-564.
17. Burri RJ, Stone NN, Unger P, Stock RG. Long-term outcome and toxicity of salvage brachytherapy for local failure after initial radiotherapy for prostate cancer. International Journal of Radiation Oncology* Biology* Physics. 2010;77: 1338-1344.
18. Perrotte P, LITWIN MS, McGUIRE EJ, Scott SM, Von Eschenbach AC, Pisters LL. Quality of life after salvage cryotherapy: the impact of treatment parameters. The Journal of Urology. 1999;162: 398-402.
19. Beyer DC. Brachytherapy for recurrent prostate cancer after radiation therapy. Seminars in radiation oncology: 2003:158-165.